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(54) Title: METHOD OF USING A COX-2 INHIBITOR AND A 5-HT_{1A} RECEPTOR MODULATOR AS A COMBINATION THERAPY

(57) Abstract: Compositions and methods to treat or prevent pain, inflammation, or inflammation-related disorder, as well as a neurologic disorder involving neurodegmeration in a subject that is in need of such prevention or treatment involve a combination of a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator.

WO 2004/045509 A2

METHOD OF USING A COX-2 INHIBITOR AND A 5-HT$_{1A}$ RECEPTOR MODULATOR AS A COMBINATION THERAPY

CROSS-REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

[0001] This application is a non-provisional of United States Provisional Patent Application No. 60/427,198, filed November 18, 2002, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

(1) Field of the invention:

[0002] The present invention relates to compositions and methods for the treatment or prevention of pain, inflammation, or inflammation-related disorder in a mammal using a combination of a Cox-2 inhibitor and a 5-HT$_{1A}$ receptor modulator.

(2) Description of related art:

[0003] Serotonin (5-hydroxytryptamine, or 5-HT) is involved in the origin of many disease states. Recently, at least fourteen different 5-HT receptor subtypes have been identified and characterized ("A Review of Central 5-HT Receptors and Their Function," N. M. Barnes and T. Sharp, *Neuropharmacology, 38:*1083-1152 (1999)). The 5-HT$_1$ receptor family consists of five receptor subtypes: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, and 5-HT$_{1F}$. The 5-HT$_{1A}$ receptor is the best known among the different 5-HT receptors and is widely distributed in the central nervous system (L. Lanfurney and M. Hamon, *Nuclear Medicine & Biology, 27:*429-435 (2000)).

[0004] Studies on the 5-HT$_{1A}$ receptor have shown potential roles in a variety of physiological processes including, neuroendocrine function, thermoregulation, vasoreactive headaches, sexual behavior, food intake, tooth-germ morphogenesis, immune function, aggression, depression and anxiety (J. R. Raymond, *et al., Br. J. Pharmacol., 127:*1751-1764 (1999)). Other studies have shown the potential use of 5-HT$_{1A}$ agonists in

glaucoma to lower intraocular pressure in the eye (N. N. Osborne, *et al., Eye, 14*:454-463 (2000)). Recent studies have shown the involvement of 5-HT_{1A} receptors in the transmission of nociceptive (pain) information in the spinal cord resulting from nerve injury or inflammation (Z.-Y. Liu, *et al, Neuroscience, 112(2)*:399-407 (2002)). Growing evidence suggests that the 5-HT_{1A} receptor is important in learning and memory processes (A. Meneses, *Neurosci. Biobehav. Rev., 23*:1111-1125 (1999)) and that 5-HT_{1A} receptor antagonists may have utility in treating cognitive dysfunction associated with Alzheimer's disease (L. E. Schechter, *et al., Curr. Pharm. Des., 8(2)*:139-145 (2002)). A 5-HT_{1A} receptor agonist has shown a neuroprotective effect associated with its ability to inhibit ischemia-induced release of glutamate in the brain in a stroke model (I. Semkova, *et al., Eur. J. Pharmacol., 359*:251-260 (1998)).

[0005] Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG_2, PGH_2 and PGE_2, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (Cox). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (Cox-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

[0006] Compounds that selectively inhibit the cyclooxygenase-2 enzyme have been discovered. These compounds selectively inhibit the activity of Cox-2 to a greater extent than the activity of Cox-1. The Cox-2-selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, cyclooxygenase-2-selective inhibitors have shown great promise for use in therapies -- especially in therapies that require extended administration, such as for pain and inflammation control for arthritis. Additional information on the identification of cyclooxygenase-2-selective inhibitors can be found in: (1) Buttgereit, F. *et al., Am. J. Med., 110(3 Suppl. 1)*:13-9 (2001); (2) Osiri, M. *et al, Arthritis Care Res., 12(5)*:351-62 (1999); (3) Buttar, N.S. *et al., Mayo Clin. Proc., 75(10)*:1027-38 (2000); (4) Wollheim, F. A., *Current Opin. Rheumatol., 13*:193-201 (2001); (5) U.S. Patent Nos. 5,434,178 (1,3,5-trisubstituted pyrazole compounds); (6) 5,476,944 (derivatives of cyclic phenolic thioethers); (7) 5,643,933 (substituted sulfonylphenylheterocycles); 5,859,257 (isoxazole compounds); (8) 5,932,598 (prodrugs of benzenesulfonamide-containing Cox-2 inhibitors); (9) 6,156,781 (substituted pyrazolyl benzenesulfonamides); and (10) 6,110,960 (for dihydrobenzopyran and related compounds).

[0007] Cox-2 inhibitors have also been described for the treatment of cancer (WO98/16227) and for the treatment of tumors (See, EP 927,555, and Rozic *et al., Int. J. Cancer, 93(4)*:497 - 506 (2001)). Celecoxib, a selective inhibitor of Cox-2, exerted a potent inhibition of fibroblast growth factor-induced corneal angiogenesis in rats. (Masferrer *et al., Proc. Am. Assoc. Cancer Research 1999, 40:* 396). WO 98/41511 describes 5-(4-sulphonyl-phenyl)-pyridazinone derivatives used for treating cancer. WO 98/41516 describes (methylsulphonyl)phenyl-2-(5H)-furanone derivatives that can be used in the treatment of cancer. Kalgutkar, A. S. *et al., Curr. Drug Targets, 2(1)*:79 - 106 (2001) suggest that Cox-2 selective inhibitors could be used to prevent or treat cancer by affecting tumor viability, growth, and metastasis. Masferrer *et al.*, in *Ann. NY Acad. Sci., 889*:84 -

86 (1999) describe Cox-2 selective inhibitors as antiangiogenic agents with potential therapeutic utility in several types of cancers. The utility of Cox-2 inhibition in clinical cancer prevention was described by Lynch, P. M., in *Oncology, 15(3)*:21 - 26 (2001), and Watanabe *et al.*, in *Biofactors 2000, 12(1 - 4)*:129 - 133 (2000) described the potential of Cox-2 selective inhibitors for chemopreventive agents against colon cancer.

[0008] Additionally, various combination therapies using Cox-2 inhibitors with other selected combination regimens for the treatment of cancer have also been reported. See *e.g.*, FR 27 71 005 (compositions containing a cyclooxygenase-2 inhibitor and N- methyl-d-aspartate (NMDA) antagonist used to treat cancer and other diseases); WO 99/18960 (combination comprising a cyclooxygenase-2 inhibitor and an inducible nitric-oxide synthase inhibitor (iNOS) that can be used to treat colorectal and breast cancer); WO 99/13799 (combination of a cyclooxygenase-2 inhibitor and an opioid analgesic); WO 97/36497 (combination comprising a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor useful in treating cancer); WO 97/29776 (composition comprising a cyclooxygenase-2 inhibitor in combination with a leukotriene B4 receptor antagonist and an immunosuppressive drug); WO 97/29775 (use of a cyclooxygenase-2 inhibitor in combination with a leukotriene A4 hydrolase inhibitor and an immunosuppressive drug); WO 97/29774 (combination of a cyclooxygenase-2 inhibitor and prostagladin or antiulcer agent useful in treating cancer); WO 97/11701 (combination comprising of a cyclooxygenase-2 inhibitor and a leukotriene B receptor antagonist useful in treating colorectal cancer); WO 96/41645 (combination comprising a cyclooxygenase-2 inhibitor and leukotriene A hydrolase inhibitor); WO 96/03385 (3,4,-Di substituted pyrazole compounds given alone or in combination with NSAIDs, steroids, 5-LO inhibitors, LTB4 antagonists, or LTA4 hydrolase inhibitors for the treatment of cancer); WO 98/47890 (substituted benzopyran derivatives that may be used alone or in combination with other active principles); WO 00/38730 (method of using cyclooxygenase-2 inhibitor and one or more

antineoplastic agents as a combination therapy in the treatment of neoplasia); Mann, M. *et al., Gastroenterology, 120(7)*:1713 - 1719 (2001) (combination treatment with Cox-2 and HER-2/neu inhibitors reduced colorectal carcinoma growth).

[0009] Other reports have indicated the Cox-2 selective inhibitors have cardiovascular applications. For example, Saito, T. *et al.,* in *Biochem. Biophys. Res. Comm., 273*:772 - 775 (2000), reported that the inhibition of Cox-2 improves cardiac function in myocardial infarction. Ridker, P.M. *et al.,* in *The New England J. of Med., 336(14)*:973 - 979 (1997), raised the possibility that anti-inflammatory agents may have clinical benefits in preventing cardiovascular disease. In addition, Cox-2 selective inhibitors have been proposed for therapeutic use in cardiovascular disease when combined with modulation of inducible nitric oxide synthase (See, Baker, C. S. R. *et al., Arterioscler. Thromb. Vasc. Biol., 19*:646-655 (1999)), and with HMG-CoA reductase inhibitor (U.S. Patent No. 6,245,797).

[00010] Recent studies have shown that Cox-2 and its reaction products participate in ischemic injury in the human brain caused by stroke or other injury (C. Iadecola, *et al., Proc. Natl. Acad. Sci. U.S.A., 98(3)*:1294-1299 (2001)). A selective Cox-2 inhibitor has been shown to be neuroprotective, resulting in improvements in behavorial deficits caused by spinal cord ischemia (P. A. Lapchak, *et al., Stroke, 32*:1220-1225 (2001)). Studies have shown that Cox-2 expression is elevated in Alzheimer's disease brains, is correlated with dementia, and causes detrimental alterations of the neuronal cell cycle (Xiang *et al., Neurobiol. Aging, 23*:327-334 (2002)).

[00011] EP 1064967 describes the combination of 5-HT_{1A} receptor agonists, caffeine, and either a Cox-2 inhibitor or NSAID for the treatment of migraine.

[00012] EP 1064966 describes the combination of a 5-HT_{1A} receptor agonist, caffeine, and a Cox-2 inhibitor for the treatment of migraine.

[00013] EP 1064948 describes the combination of a 5-HT_{1A} receptor antagonist, caffeine, and a Cox-2 inhibitor for the treatment of migraine.

[00014] EP 1051995 describes the combination of 5-HT_{1A} receptor agonists and either a Cox-2 inhibitor or NSAID for the treatment of migraine.

[00015] EP 1051994 describes the combination of a 5-HT_{1A} agonist and a Cox-2 inhibitor for the treatment of migraine.

[00016] EP 1051993 describes the combination of 5-HT_{1A} receptor agonists and either a Cox-2 inhibitor or NSAID for the treatment of migraine.

[00017] US 20020077328 describes the combination of selective Cox-2 inhibitors and vasomodulator compounds for generalized pain and headache pain.

[00018] WO 0048583 describes the combination of 5-HT agonists with Cox-2 inhibitors for the treatment of migraine.

[00019] U.S. Patent Nos. 6,420,432, 6,413,961, 6,261,279, 6,254,585, 6,242,447, 6,210,394, 6,056,715, 5,860,950, 5,858,017, 5,820,583, and 5,800,385 describe various types of irrigation solution and a method for inhibition of pain and inflammation, where the solutions can contain a Cox-2 inhibitor and some type of serotonin agonist or 5-HT_{1A} receptor agonist.

[00020] In U.S. Patent Publication No. 2002/0077328 A1, Hassan *et al.* disclose, among other things, a method for treatment of headache symptoms by administering a selective Cox-2 inhibitor and a vasomodulator, where the IC_{50} of the combination for binding of $5TH_{1A}$ [HT_{1A}] receptors is at least about 250 nM.

[00021] A need remains, however, for an improved method of treating and preventing pain, inflammation or inflammation-related disorders, and also for treating and preventing neorologic disorders involving neurodegeneration. In particular, it would be useful to provide such a method by utilizing a combination of therapeutic agents that is more efficacious and safer that presently available methods.

SUMMARY OF THE INVENTION

[00022] Briefly, therefore, the present invention is directed to a novel composition comprising a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator.

[00023] The present invention is also directed to a novel method for the treatment or prevention of pain, inflammation, or inflammation-related disorder in a mammal in need thereof, comprising administering to the mammal a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator.

[00024] The present invention is also directed to a novel pharmaceutical composition for the treatment or prevention of pain, inflammation, or inflammation-related disorder, the pharmaceutical composition comprising a Cox-2 inhibitor, a 5-HT_{1A} receptor modulator, and a pharmaceutically-acceptable excipient.

[00025] The present invention is also directed to a novel kit that is suitable for use in the treatment or prevention of pain, inflammation, or inflammation-related disorder wherein the kit comprises a first dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a 5-HT_{1A} receptor modulator, in quantities which comprise a therapeutically effective amount of the compounds for the treatment or prevention of pain, inflammation, or inflammation-related disorder.

[00026] The present invention is also directed to a novel method for the treatment or prevention of neurologic disease involving neurodegeneration in a mammal in need thereof, comprising administering to the mammal a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator.

[00027] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of an improved method of treating or preventing pain, inflammation or inflammation-related disorders, and treatment or prevention of neurologic diseases involving neurodegeneration, the provision of such a method by utilizing a combination of therapeutic agents that is more efficacious and safer than

methods and compositions that are presently available, and the provision of therapeutic combinations and methods for the prevention and treatment of pain, inflammation and inflammation-related disorders.

DETAILED DESCRIPTION OF THE INVENTION

[00028] In accordance with the present invention, it has been discovered that pain, inflammation, or inflammation-related disorders in a subject -- in particular, a mammal -- can be treated or prevented by a combination therapy method that involves administering to the subject an amount of a Cox-2 inhibitor and an amount of a 5-HT_{1A} receptor modulator. In preferred embodiments, the amount of the Cox-2 inhibitor and the amount of the 5-HT_{1A} receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation or inflammation-related disorder in the subject.

[00029] Also disclosed herein is a composition comprising an amount of a Cox-2 inhibitor and an amount of a 5-HT_{1A} receptor modulator wherein the amount of the Cox-2 inhibitor and the amount of the 5-HT_{1A} receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation or inflammation-related disorder.

[00030] A component of the present invention is a Cox-2 inhibitor. The terms "cyclooxygenase-2 inhibitor", or "Cox-2 inhibitor", which can be used interchangeably herein, embrace compounds which inhibit the Cox-2 enzyme regardless of the degree of inhibition of the Cox-1 enzyme, and include pharmaceutically acceptable salts of those compounds. Thus, for purposes of the present invention, a compound is considered a Cox-2 inhibitor irrespective of whether the compound inhibits the Cox-2 enzyme to an equal, greater, or lesser degree than the Cox-1 enzyme.

[00031] In one embodiment of the present invention, it is preferred that the Cox-2 inhibitor compound is a non-steroidal anti-inflammatory drug (NSAID). Therefore, preferred materials that can serve as the Cox-2 inhibitor of the present invention include non-steroidal anti-inflammatory

drug compounds, a pharmaceutically acceptable salt thereof, or a pure (-) or (+) optical isomeric form thereof.

[00032] Examples of NSAID compounds that are useful in the present invention include acemetacin, acetyl salicylic acid, alclofenac, alminoprofen, azapropazone, benorylate, benoxaprofen, bucloxic acid, carprofen, choline magnesium trisalicylate, clidanac, clopinac, dapsone, diclofenac, diflunisal, droxicam, etodolac, fenoprofen, fenbufen, fenclofenec, fentiazac, floctafenine, flufenisal, flurbiprofen, (r)-flurbiprofen, (s)-flurbiprofen, furofenac, feprazone, flufenamic acid, fluprofen, ibufenac, ibuprofen, indometacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, miroprofen, piroxicam, meloxicam, mefenamic, mefenamic acid, meclofenamic acid, meclofen, nabumetone, naproxen, niflumic acid, oxaprozin, oxipinac, oxyphenbutazone, phenylbutazone, podophyllotoxin derivatives, proglumetacin, piprofen, pirprofen, prapoprofen, salicylic acid, salicylate, sudoxicam, suprofen, sulindac, tenoxicam, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, zidometacin, zomepirac, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

[00033] In a preferred embodiment, the Cox-2 inhibitor is a Cox-2 selective inhibitor. The term "Cox-2 selective inhibitor" embraces compounds which selectively inhibit the Cox-2 enzyme over the Cox-1 enzyme, and also include pharmaceutically acceptable salts and prodrugs of those compounds.

[00034] In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of Cox-1, divided by the IC_{50} value for inhibition of Cox-2 (Cox-1 IC_{50}/Cox-2 IC_{50}). A Cox-2 selective inhibitor is any inhibitor for which the ratio of Cox-1 IC_{50} to Cox-2 IC_{50} is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably

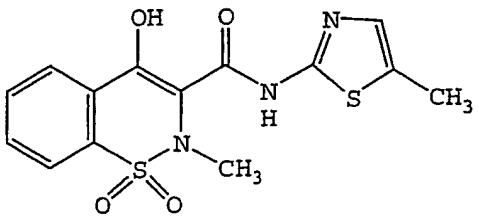
greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

[00035] As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred Cox-2 selective inhibitors of the present invention have a Cox-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

[00036] Preferred Cox-2 selective inhibitors have a Cox-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

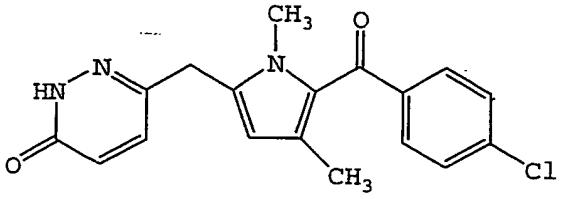
[00037] Also included within the scope of the present invention are compounds that act as prodrugs of Cox-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is sodium parecoxib. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

[00038] The Cox-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-1

[00039] In another embodiment of the invention the Cox-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



B-2

[00040] As used herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; embraces linear or branched radicals having one to about twenty carbon atoms. Lower alkyl radicals have one to about ten carbon atoms. The number of carbon atoms can also be expressed as "C_1-C_5", for example. Examples of lower alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the, like.

[00041] The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. The alkenyl radicals may be optionally substituted with groups such as those defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropylenyl, buten-1yl, isobutenyl, penten-1yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like.

[00042] The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups such as described below. Examples of suitable alkynyl radicals include ethynyl, proynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-

methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

[00043] The term "oxo" means a single double-bonded oxygen.

[00044] The terms "hydrido", "-H", or "hydrogen", denote a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical, or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical.

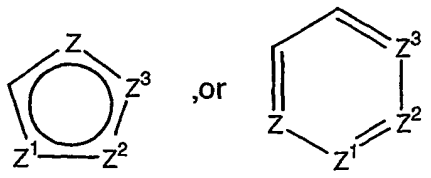
[00045] The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo alkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

[00046] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

[00047] The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and diaikoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy.

[00048] The term "aryl", whether used alone or with other terms, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner, or may be fused. The term "aryl" embraces aromatic radicals such as phenyl,

naphthyl, tetrahydronapthyl, indane, and biphenyl. The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms are replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z^1, Z^2, or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others.

[00049] The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals include thienyl, pyrryl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

[00050] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The term "aminosulfonyl"denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2-NH_2$).

[00051] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2-H$. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes – (C=O) –. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is CH_3 – (CO) –. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3$-C-O–C=O) – and – (O=)C– OCH_3. The term "amino", whether used alone or with other terms, such as "aminocarbonyl", denotes $-NH_2$.

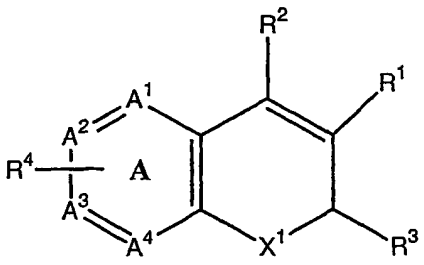
[00052] The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The terms "aralkyl", or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cylopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[00053] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3 –S–). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent –S(–O) – atom. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid.

[00054] The term "cyano", used either alone or with other terms, such as "cyanoalkyl", refers to C≡N. The term "nitro" denotes $-NO_2$.

[00055] In one embodiment of the invention the Cox-2 selective inhibitor is of the chromene/chroman structural class, which encompasses substituted benzopyrans or substituted benzopyran analogs, as well as substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the general Formulas I, II, III, IV, V, and VI, shown below, and including, by way of non-limiting example, the structures disclosed in Table 1, and the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00056] Benzopyrans that can serve as a Cox-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent Nos. 6,271,253 and 6,492,390. One such class of compounds is defined by the general formula shown below in formula **I**:



I

wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, acyl and carboxy-C_1 –C_6 –alkyl;

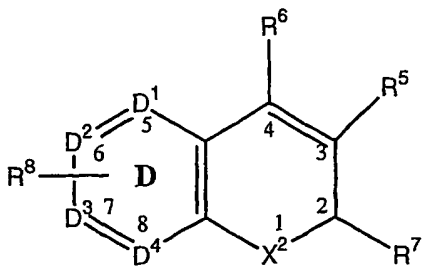
wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1 –C_6 –alkyl and C_2 –C_6 –alkenyl;

wherein R^3 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 – alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;
wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 – alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 – C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-$_1$ – C_3 –hydroxyalkyl, C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 – C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 – C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 – alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_1 –alkoxycarbonyl, formyl, C_1 –C_6 – haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and
wherein the A ring atoms A^1, A^2, A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1, A^2, A^3 and A^4 are carbon;
or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;
or an isomer or pharmaceutically acceptable salt thereof.

[00057] Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes compounds having the structure of formula II:



II

wherein X^2 is selected from O, S, $CR^c R^b$ and NR^a;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C_1 –C_6 –alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

or wherein $CR^c R^b$ form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 –C_6 –alkynyl and C_2 –C_6 –alkenyl;

wherein R^7 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, —$O(CF_2)_2O$—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-C_1 –C_3 –hydroxyalkyl), C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 –C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl,

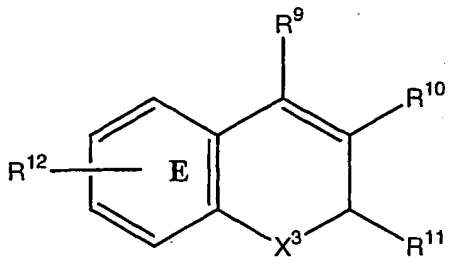
heteroarylaminosulfonyl, aryl-C_1 –C_6 –alkylaminosulfonyl, heteroaryl-C_1 – C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 –alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_6 –alkoxycarbonyl, formyl, C_1 –C_6 –haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the D ring atoms D^1, D^2, D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1, D^2, D^3 and D^4 are carbon; or

wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;

or an isomer or pharmaceutically acceptable salt thereof.

[00058] Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula **III**:



III

wherein X^3 is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

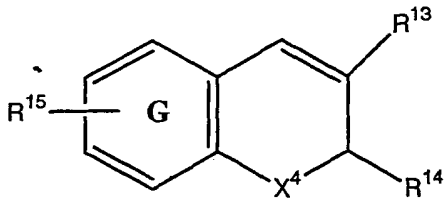
wherein R^9 is selected from the group consisting of H and aryl;

wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and
including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00059] A related class of compounds useful as Cox-2 selective inhibitors in the present invention is described by Formulas **IV** and **V** below:



IV

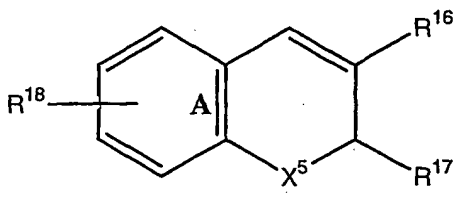
wherein X^4 is selected from O or S or NR^a ;
wherein R^a is alkyl;
wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and
wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino,

heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00060] Formula **V** is:



V

wherein:

X^5 is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl,

aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00061] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00062] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower

aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00063] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00064] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

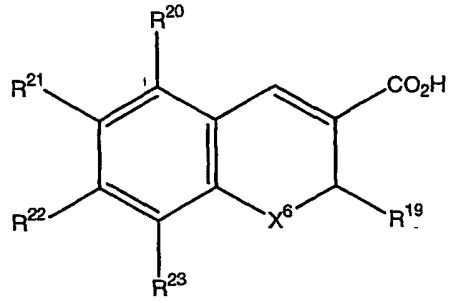
R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

[00065] The Cox-2 selective inhibitor of the present invention can also be a compound having the structure of Formula **VI**:



VI

wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

[00066] The Cox-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

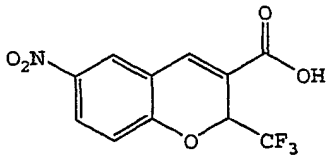
R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

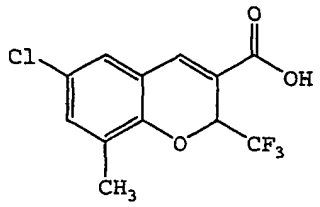
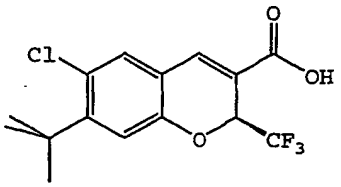
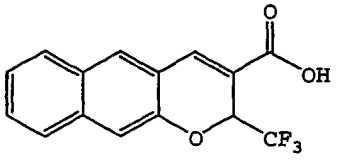
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

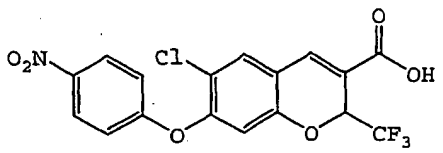
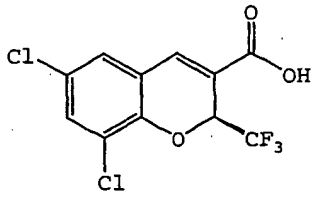
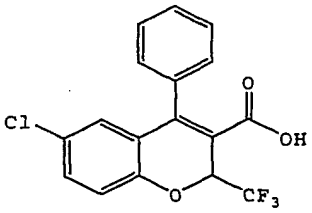
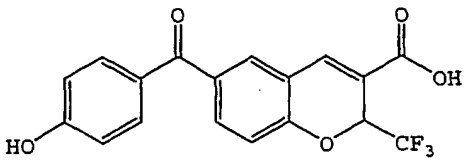
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

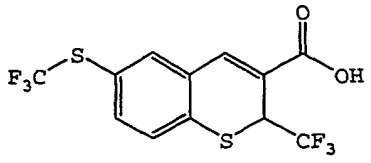
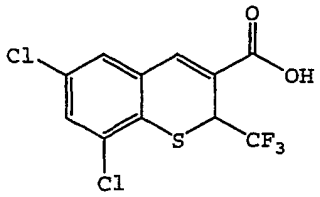
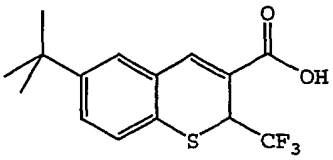
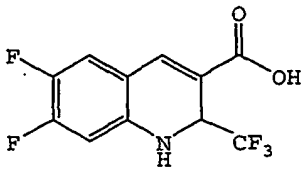
or an isomer or prodrug thereof.

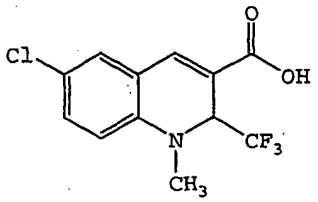
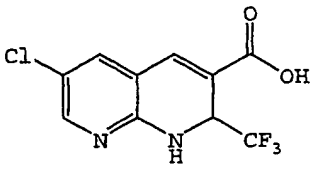
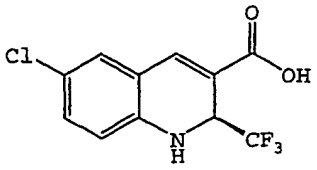
Table 1. Examples of Chromene Cox-2 Selective Inhibitors

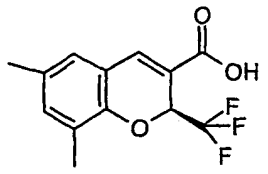
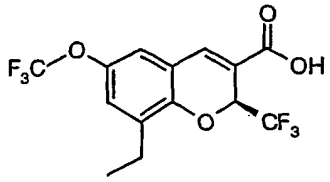
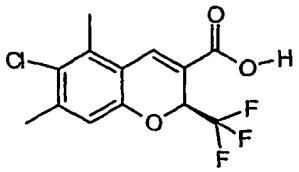
Compound Number	**Structural Formula**
B-3	 6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-4	 6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid

Compound Number	Structural Formula
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

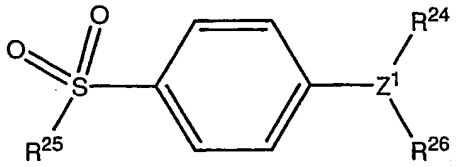
Compound Number	Structural Formula
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-18	 (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid
B-19	 (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid
B-20	 (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

[00067] In preferred embodiments the chromene Cox-2 inhibitor is selected from (S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-6-chloro-8-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6-chloro-5,7-

dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, and mixtures thereof.

[00068] In a preferred embodiment of the invention the Cox-2 inhibitor can be selected from the class of tricyclic Cox-2 selective inhibitors represented by the general structure of formula **VII**:



VII

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino,

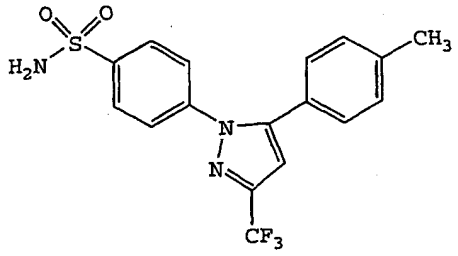
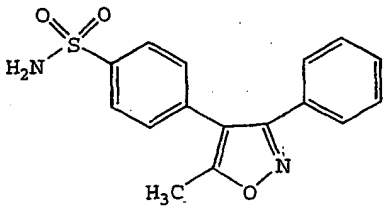
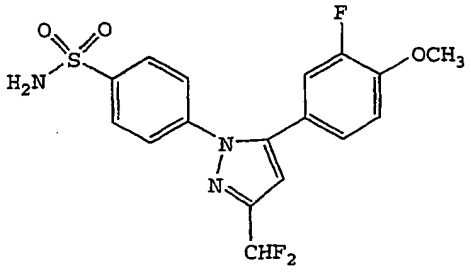
aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

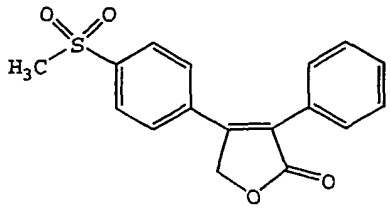
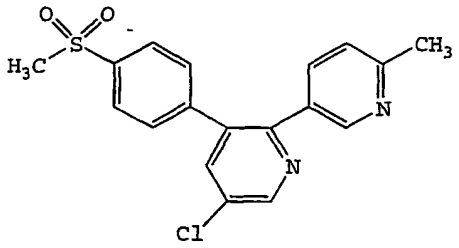
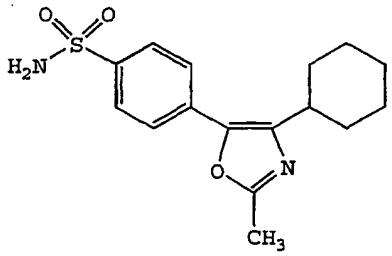
or a prodrug thereof.

[00069] In a preferred embodiment of the invention the Cox-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-21), valdecoxib (B-22), deracoxib (B-23), rofecoxib (B-24), etoricoxib (MK-663; B-25), JTE-522 (B-26), or prodrugs thereof.

[00070] Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

Table 2. Examples of Tricyclic COX-2 Selective Inhibitors

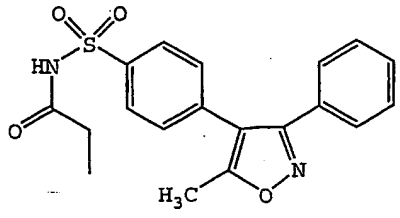
Compound Number	Structural Formula
B-21	
B-22	
B-23	

Compound Number	Structural Formula
B-24	
B-25	
B-26	

[00071] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

[00072] In a preferred embodiment, parecoxib (See, U.S. Patent No. 5,932,598), having the structure shown in B-27, and which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor

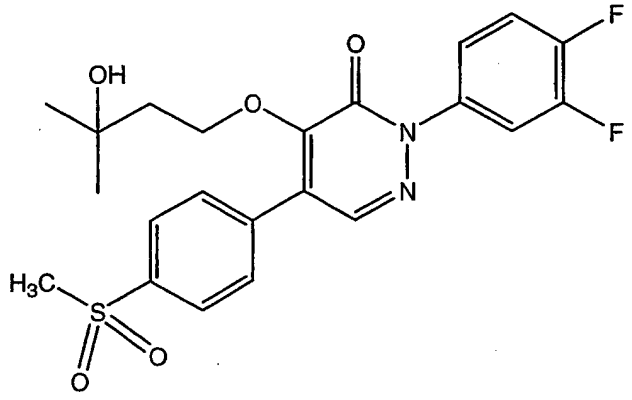
valdecoxib, B-22, (See, U.S. Patent No. 5,633,272), may be advantageously employed as the Cox-2 inhibitor of the present invention.



B-27

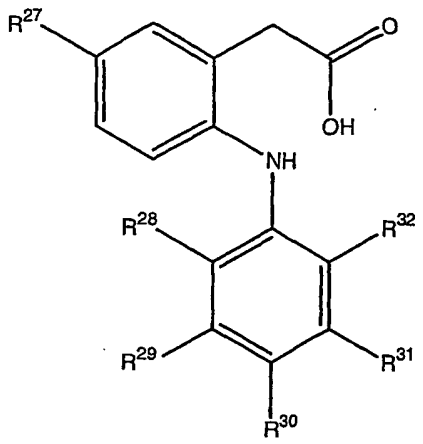
[00073] A preferred form of parecoxib is sodium parecoxib.

[00074] Another tricyclic Cox-2 selective inhibitor useful in the present invention is the compound ABT-963, having the formula B-28 shown below, that has been previously described in International Publication Number WO 00/24719.



B-28

[00075] In a further embodiment of the invention, the Cox-2 inhibitor can be selected from the class of phenylacetic acid derivative Cox-2 selective inhibitors represented by the general structure of formula **VIII**:



VIII

wherein:

R^{27} is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxyl;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28}, R^{29}, R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

[00076] An exemplary phenylacetic acid derivative Cox-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

[00077] Another phenylacetic acid derivative Cox-2 selective inhibitor is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

[00078] Another phenylacetic acid derivative Cox-2 selective inhibitor that is disclosed in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib; CAS Reg. No. 220991-20-8), having the structure shown in formula **VIII**,

wherein:

R^{27} is methyl;

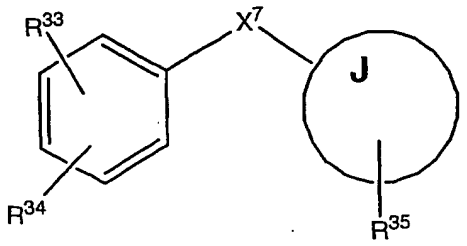
R^{28} is fluoro;

R^{32} is chloro; and

R^{29}, R^{30}, and R^{31} are hydrogen.

[00079] Compounds having a structure similar to that shown in formula **VIII**, that can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,451,858, 6,310,099, 6,291,523, and 5,958,978.

[00080] Other Cox-2 selective inhibitors that can be used in the present invention have the general structure shown in formula **IX**, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



IX

wherein:

X^7 is O; J is 1-phenyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 4-NO_2; and there is no R^{35} group, (nimesulide), or

X^7 is O; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$NHSO_2CH_3$, (flosulide); or

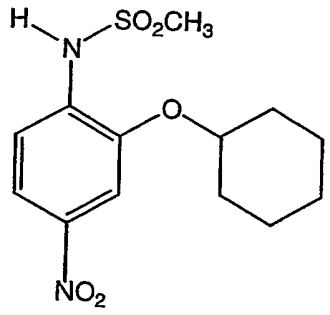
X^7 is O; J is cyclohexyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 5-NO_2; and there is no R^{35} group, (NS-398); or

X^7 is S; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); or

X^7 is S; J is thiophen-2-yl; R^{33} is 4-F; there is no R^{34} group; and R^{35} is 5-$NHSO_2CH_3$, (RWJ-63556); or

X^7 is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

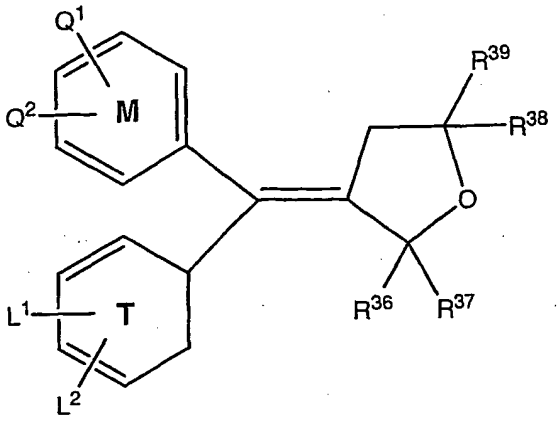
[00081] The Cox-2 selective inhibitor NS-398, also known as N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (CAS RN 123653-11-2), having a structure as shown below in formula B-29, has been described in, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res., 90(4):*406 – 412 (1999).



B-29

[00082] An evaluation of the anti-inflammatory activity of the Cox-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

[00083] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **X**:



X

wherein:

the rings T and M independently are a phenyl radical, a naphthyl radical, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q^1, Q^2, L^1 or L^2 is an —$S(O)_n$—R group, in which n is an integer equal to 0, 1 or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an $-SO_2NH_2$ group;

and is located in the para position,

the others independently being a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a trifluoromethyl radical, or a lower O-alkyl radical having 1 to 6 carbon atoms, or Q^1 and Q^2 or L^1 and L^2 are a methylenedioxy group; and

R^{36}, R^{37}, R^{38} and R^{39} independently are a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{36}, R^{37} or R^{38}, R^{39} are an oxygen atom; or

R^{36}, R^{37} or R^{38}, R^{39}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

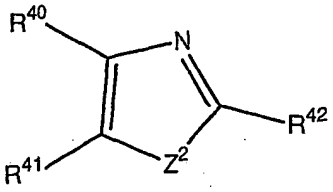
[00084] Particular diarylmethylidenefuran derivatives that can serve as the Cox-2 selective inhibitor of the present invention include, for example, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

[00085] Other Cox-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[00086] Compounds that may act as Cox-2 selective inhibitors of the present invention include multibinding compounds containing from 2 to 10 ligands covanlently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

[00087] Conjugated linoleic, as described in U.S. Patent No. 6,077,868, is useful as a Cox-2 selective inhibitor in the present invention.

[00088] Compounds that can serve as a Cox-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula **XI**:

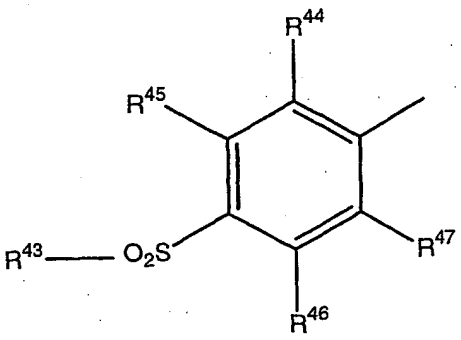


XI

wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula



wherein:

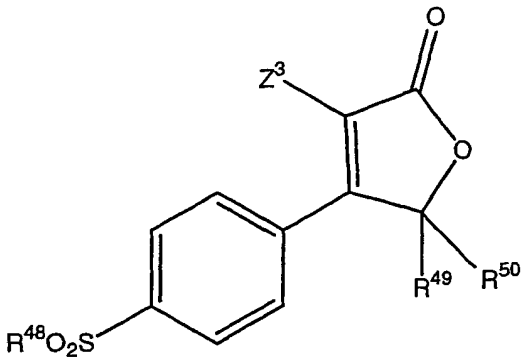
R^{43} is lower alkyl, amino or lower alkylamino; and

R^{44}, R^{45}, R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxyl or amino, provided that at least one of R^{44}, R^{45}, R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

R^{30} is a lower alkyl or a halogenated lower alkyl,

and a pharmaceutically acceptable salt thereof.

[00089] Cox-2 selective inhibitors that are useful in the method and compositions of the present invention include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



XII

wherein:

Z^3 is selected from the group consisting of linear or branched C_1 –C_6 alkyl, linear or branched C_1 –C_6 alkoxy, unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of hydrogen, halo, C_1 –C_3 alkoxy, CN, C_1 –C_3 fluoroalkyl C_1 –C_3 alkyl, and –CO_2 H;

R^{48} is selected from the group consisting of NH_2 and CH_3,

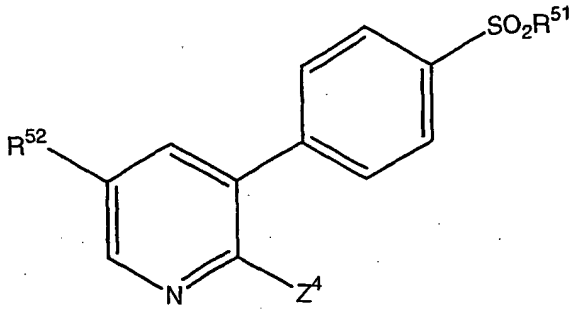
R^{49} is selected from the group consisting of C_1 –C_6 alkyl unsubstituted or substituted with C_3 –C_6 cycloalkyl, and C_3 –C_6 cycloalkyl;

R^{50} is selected from the group consisting of:

C_1 –C_6 alkyl unsubstituted or substituted with one, two or three fluoro atoms, and C_3 –C_6 cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

[00090] Pyridines that are described in U.S. Patent Nos. 6,596,736, 6,369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and can seve as Cox-2 selective inhibitors of the present invention, have the general formula described by formula **XIII**:



XIII

wherein:

R^{51} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

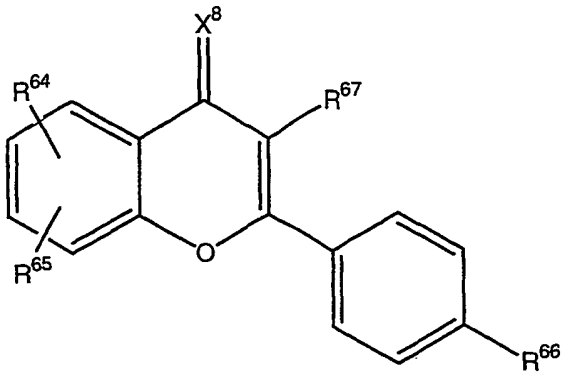
Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof), wherein the substituents are chosen from the group consisting of hydrogen, halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, –CO_2R^{53}, hydroxyl, –$C(R^{54})(R^{55})$—OH, – C_1 –C_6 alkyl-CO_2—R^{56}, C_1 –C_6 fluoroalkoxy;

R^{52} is chosen from the group consisting of: halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, —CO_2R^{57}, hydroxyl, —$C(R^{58})(R^{59})$—OH, — C_1 –C_6 alkyl-CO_2—R^{60}, C_1 –C_6 fluoroalkoxy, NO_2, $NR^{61}R^{62}$, and $NHCOR^{63}$;

R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, and R^{63}, are each independently chosen from the group consisting of hydrogen andC_1 –C_6 alkyl;

or R^{54} and R^{55}, R^{58} and R^{59}, or R^{61} and R^{62} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

[00091] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



XIV

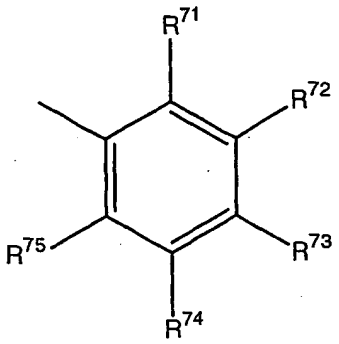
wherein:

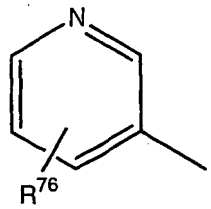
X^8 is an oxygen atom or a sulfur atom;

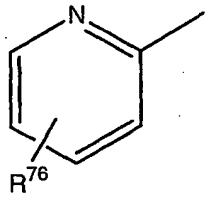
R^{64} and R^{65}, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a nitro group, a nitrile group, or a carboxyl group;

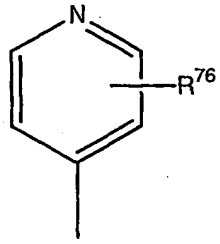
R^{66} is a group of a formula: $S(O)_nR^{68}$ wherein n is an integer of 0~2, R^{68} is a hydrogen atom, a C_1 –C_6 lower alkyl group, or a group of a formula: NR^{69} R^{70} wherein R^{69} and R^{70}, identical to or different from each other, are independently a hydrogen atom, or a C_1 –C_6 lower alkyl group; and

R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_1 –C_6 lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:









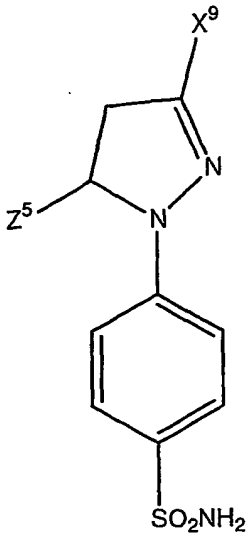
wherein:

R^{71} through R^{75}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: NR^{69} R^{70}, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,

wherein n, R^{68}, R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

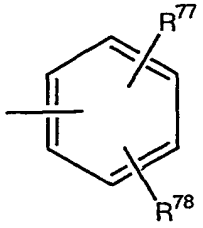
[00092] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:



XV

wherein:

X^9 is selected from the group consisting of C_1 –C_6 trihalomethyl, preferably trifluoromethyl; C_1 –C_6 alkyl; and an optionally substituted or di-substituted phenyl group of formula **XVI**:



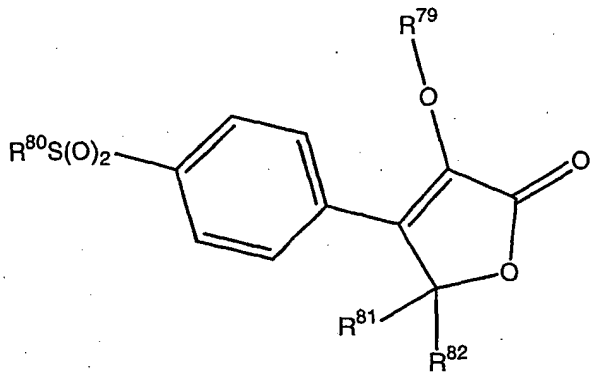
XVI

wherein:

R^{77} and R^{78} are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C_1 –C_6 alkyl, preferably C_1 –C_3 alkyl; C_1 –C_6 alkoxy, preferably C_1 – C_3 alkoxy; carboxy; C_1 –C_6 trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

[00093] Compounds useful as Cox-2 selective inhibitors of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



XVII

wherein:

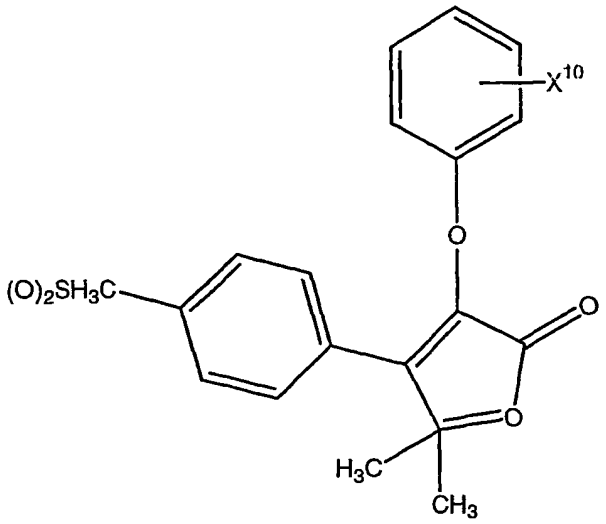
R^{79} is a mono-, di-, or tri-substituted C_1 –C_{12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted C_3 –C_{12} cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted C_5 –C_{12} cycloalkynyl, wherein the substituents are chosen from the group consisting of halo selected from F, Cl, Br, and I, OH, CF_3, C_3 – C_6 cycloalkyl, =O,dioxolane, CN;

R^{80} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

R^{81} and R^{82} are independently chosen from the group consisting of hydrogen and C_1 –C_{10} alkyl;

or R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

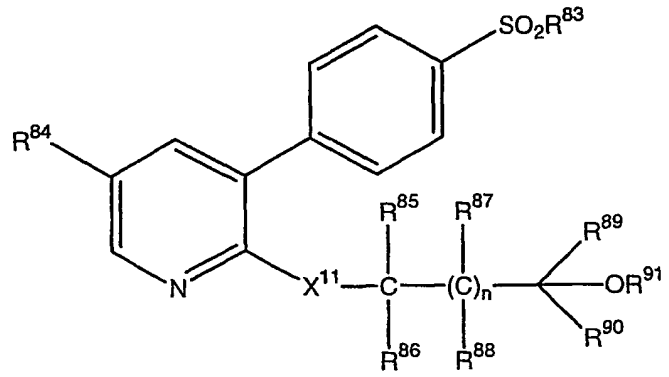
[00094] Formula **XVIII** is:



XVIII

wherein X^{10} is fluoro or chloro.

[00095] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



XIX

or a pharmaceutically acceptable salt thereof,

wherein:

X^{11} is selected from the group consisting of O, S, and a bond;

n is 0 or 1;

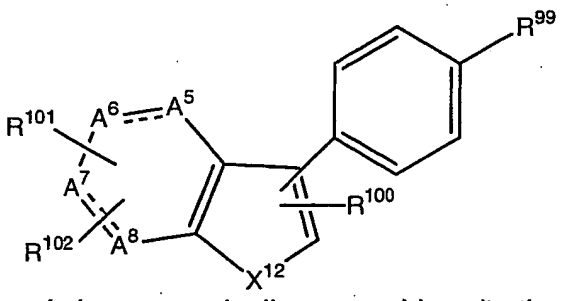
R^{83} is selected from the group consisting of CH_3, NH_2, and $NHC(O)CF_3$;

R^{84} is chosen from the group consisting of halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, —CO_2 R^{92}, hydroxyl, —$C(R^{93})(R^{94})$—OH, —C_1 –C_6 alkyl-CO_2 —R^{95}, C_1 –C_6 fluoroalkoxy, NO_2, NR^{96} R^{97}, and $NHCOR^{98}$;

R^{85} to R^{89} are independently chosen from the group consisting of hydrogen and C_1 –C_6 alkyl;

or R^{85} and R^{89}, or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond.

[00096] Compounds that are useful as the Cox-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



XX

and pharmaceutically acceptable salts thereof wherein:

—A^5=A^6—A^7=A^8— is selected from the group consisting of:

(a) —CH=CH—CH=CH—,

(b) —CH_2 —CH_2 —CH_2 —C(O)—, —CH_2 —CH_2 —C(O)—CH_2 —, —CH_2 —C(O)—CH_2 —CH_2, —C(O)—CH_2 —CH_2 —CH_2,

(c) —CH_2 —CH_2 —C(O)—, —CH_2 —C(O)—CH_2 —, —C(O)—CH_2 —CH_2 —

(d) —CH_2 —CH_2 —O—C(O)—, CH_2 —O—C(O)—CH_2 —, —O—C(O)—CH_2 —CH_2 —,

(e) —CH_2 —CH_2 —C(O)—O—, —CH_2 —C(O)—OCH_2 —, —C(O)—O—CH_2 —CH_2 —,

(f) —$C(R^{105})_2$ —O—C(O)—, —C(O)—O—$C(R^{105})_2$ —, —O—C(O)—$C(R^{105})_2$ —, —$C(R^{105})_2$ —C(O)—O—,

(g) —N=CH—CH=CH—,

(h) —CH=N—CH=CH—,

(i) —CH=CH—N=CH—,

(j) —CH=CH—CH=N—,

(k) —N=CH—CH=N—,

(l) —N=CH—N=CH—,

(m) —CH=N—CH=N—,

(n) —S—CH=N—,

(o) —S—N=CH—,

(p) —N=N—NH—,

(q) —CH=N—S—, and

(r) —N=CH—S—;

R^{99} is selected from the group consisting of $S(O)_2CH_3$, $S(O)_2NH_2$, $S(O)_2NHCOCF_3$, $S(O)(NH)CH_3$, $S(O)(NH)NH_2$, $S(O)(NH)NHCOCF_3$, $P(O)(CH_3)OH$, and $P(O)(CH_3)NH_2$;

R^{100} is selected from the group consisting of:

(a) C_1 –C_6 alkyl,

(b) C_3 –C_7 cycloalkyl,

(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo, including F, Cl, Br, I,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —$C(R^{103})(R^{104})$—OH,

(12) —$C(R^{103})(R^{104})$—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{106};

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{103})(R^{104})$—OH, and

(10) —$C(R^{103})(R^{104})$—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of –A^5=A^6— A^7=A^8— and are selected independently from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) —Q^3 wherein Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})$OH,

(f) —O—Q^4,

(g) —S—Q^4, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^3,

(2) —O—C_1 –C_5 alkyl-Q^3,

(3) —S—C_1 –C_5 alkyl-Q^3,

(4) —C_1 –C_3 alkyl-O—C_{1-3} alkyl-Q^3,

(5) —C_1 –C_3 alkyl-S—C_{1-3} alkyl-Q^3,

(6) —C_1 –C_5 alkyl-O—Q^4,

(7) —C_1 –C_5 alkyl-S—Q^4,

wherein the substituent resides on the alkyl chain and the substituent is C_1 –C_3 alkyl, and Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})OH$ Q^4 is CO_2 —C_1 –C_4 alkyl, tetrazolyl-5-yl, or $C(R^{103})(R^{104})O$—C_1 –C_4 alkyl;

R^{103}, R^{104} and R^{105} are each independently selected from the group consisting of hydrogen and C_1 –C_6 alkyl; or

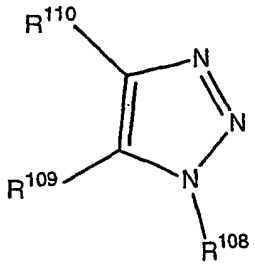
R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_1 –C_6 alkyl;

R^{107} is hydrogen, C_1 –C_6 alkyl or aryl;

X^7 is O, S, NR^{107}, CO, $C(R^{107})_2$, $C(R^{107})(OH)$, —$C(R^{107})$=$C(R^{107})$—; —$C(R^{107})$=N—; or —N=$C(R^{107})$—.

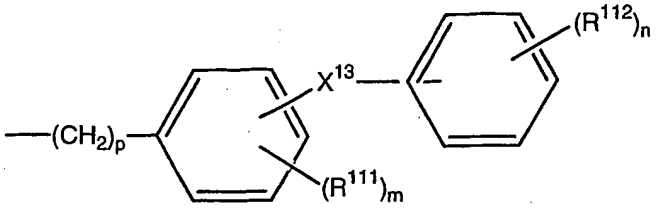
[00097] Compounds that may act as Cox-2 selective inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

R^{108} is:



wherein:

p is 0 to 2; m is 0 to 4; and n is 0 to 5;

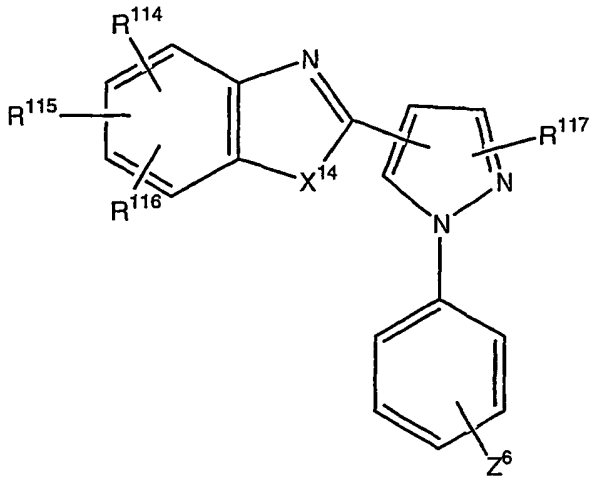
X^{13} is O, S, SO, SO_2, CO, CHCN, CH_2 or $C=NR^{113}$ where R^{113} is hydrogen, loweralkyl, hydroxyl, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano;

R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl, loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifuloromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl;

R^{109} is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, or guanidino; and

R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

[00098] Pyrazole derivatives such as those described in U.S. Patent 6,136,831 can serve as a Cox-2 selective inhibitor of the present invention. Such pyrazole derivatives have the formula shown below in formula **XXII**:



XXII

wherein:

R^{114} is hydrogen or halogen;

R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxyl or lower alkanoyloxy;

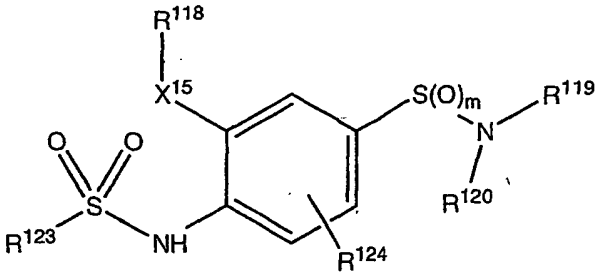
R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

[00099] Materials that can serve as a Cox-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



XXIII

wherein:

X^{15} denotes oxygen, sulphur or NH;

R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy;

R^{119} and R^{120}, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$ $-X^{16}$; or

R^{119} and R^{120}, together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$—X^{16};

X^{16} denotes halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121};

n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

R^{124} denotes halogen, hydroxyl, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121}, or a polyfluoroalkyl group;

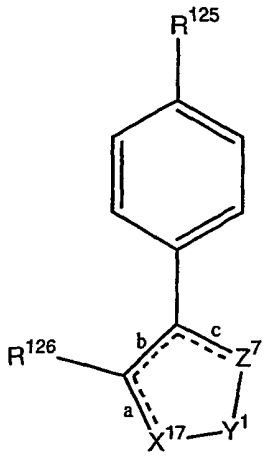
R^{121} and R^{122}, independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable salts thereof.

[000100] Compounds that are useful as Cox-2 selective inhibitors of the present invention include phenyl heterocycles that are described in U.S.

Patent Nos. 5,474,995 and 6,239,173. Such phenyl heterocyclic compounds have the formula shown below in formula **XXIV**:



XXIV

or pharmaceutically acceptable salts thereof wherein:

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) —CH_2 CH_2 CH_2 —,

(b) —C(O)CH_2 CH_2 —,

(c) —CH_2 CH_2 C(O)—,

(d) —CR^{129} ($R^{129'}$)—O—C(O)—,

(e) —C(O)—O—CR^{129} ($R^{129'}$)—,

(f) —CH_2 —NR^{127} —CH_2 —,

(g) —CR^{129} ($R^{129'}$)—NR^{127} —C(O)—,

(h) —CR^{128}=$CR^{128'}$ —S—,

(i) —S—CR^{128}=$CR^{128'}$ —,

(j) —S—N=CH—,

(k) —CH=N—S—,

(l) —N=CR^{128} —O—,

(m) —O—CR^{128} =N— ,

(n) —N=CR^{128} —NH—,

(o) —N=CR^{128} —S—, and

(p) —S—CR^{128}=N—,

(q) —C(O)—NR^{127} —CR^{129} ($R^{129'}$)—,

(r) —R^{127} N—CH=CH— provided R^{122} is not —$S(O)_2CH_3$,

(s) —CH=CH—NR^{127} — provided R^{125} is not —$S(O)_2CH_3$;

when side b is a double bond, and sides a and c are single bonds; and

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) =CH—O—CH=, and

(b) =CH—NR^{127} —CH=,

(c) =N—S—CH=,

(d) =CH—S—N=,

(e) =N—O—CH=,

(f) =CH—O—N=,

(g) =N—S—N=,

(h) =N—O—N=,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of:

(a) $S(O)_2$ CH_3,

(b) $S(O)_2$ NH_2,

(c) $S(O)_2$ $NHC(O)CF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHC(O)CF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{126} is selected from the group consisting of

(a) C_1 –C_6 alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —$C(R^{129})(R^{130})$—OH,

(12) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{129} ;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{129})(R^{130})$—OH, and

(10) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{127} is selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) hydroxyl C_1 –C_6 alkyl,

(f) —C(O)— C_1 –C_6 alkyl,

(g) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —C_1 –C_5 alkyl-O—C_1 –C_3 alkyl-Q^5,

(3) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(4) —C_1 –C_5 alkyl-O—Q^5, or

(5) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl;

(h) –Q^5;

R^{128} and $R^{128'}$ are each independently selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) –Q^5,

(f) —O—Q^5;

(g) —S—Q^5, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —O—C_1 –C_5 alkyl-Q^5,

(3) —S—C_1 –C_5 alkyl-Q^5,

(4) —C_1 –C_3 alkyl-O—C_1 –C_3 alkyl-Q^5,

(5) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(6) —C_1 –C_5 alkyl-O—Q^5,

(7) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl, and

R^{129}, $R^{129'}$, R^{130}, R^{131} and R^{132} are each independently selected from the group consisting of:

(a) hydrogen,

(b) C_1 –C_6 alkyl;

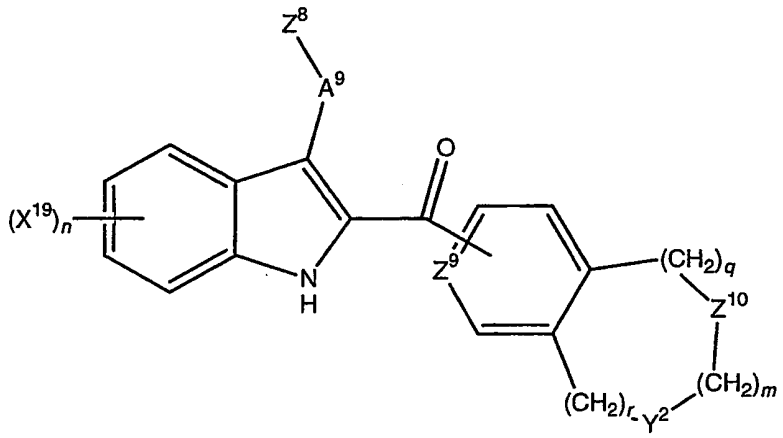
or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q^5 is CO_2H, CO_2 —C_1 –C_4 alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or $C(R^{131})(R^{132})(O—C_1$ –C_4 alkyl);

provided that when X—Y—Z is —S—CR^{128}=$CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3.

[000101] An exemplary phenyl heterocycle that is disclosed in U.S. Patent No. 6,239,173 is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(2H)-furanone.

[000102] Bicycliccarbonyl indole compounds such as those described in U.S. Patent No. 6,303,628 are useful as Cox-2 selective inhibitors of the present invention. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

or the pharmaceutically acceptable salts thereof wherein:

A^9 is C_1 –C_6 alkylene or —NR^{133} —;

Z^8 is $C(=L^3)R^{134}$, or SO_2R^{135} ;

Z^9 is CH or N;

Z^{10} and Y^2 are independently selected from —CH_2 —, O, S and —N—R^{133};

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkoxy, C_1 –C_4 alkylthio, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino and cyano;

n is 0, 1, 2, 3 or 4;

L^3 is oxygen or sulfur;

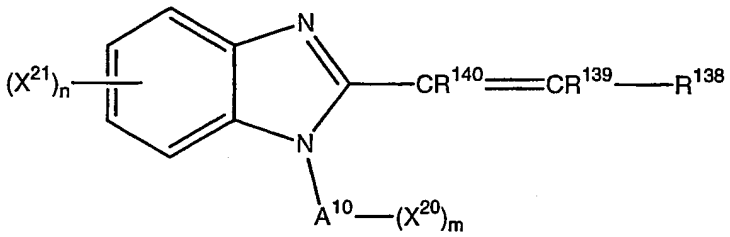
R^{133} is hydrogen or C_1 –C_4 alkyl;

R^{134} is hydroxyl, C_1 –C_6 alkyl, halo-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, halo-substituted C_1 –C_6 alkoxy, C_3 –C_7 cycloalkoxy, C_1 –C_4 alkyl(C_3 –C_7 cycloalkoxy), —NR^{136} R^{137}, C_1 –C_4 alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy and nitro;

R^{135} is C_1 –C_6 alkyl or halo-substituted C_1 –C_6 alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, $C_{1\text{-}6}$ alkyl and halo-substituted C_1 –C_6 alkyl.

[000103] Materials that can serve as a Cox-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



XXVI

or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or

a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

X^{20} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amonio, N-(C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1 –C_4 alkyl)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

X^{21} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-(C_1 –C_4 alkyl)-N-(C_1 –C_4 alkanoyl) amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)hydroxyl, cabamoyl, [N-(C_1 –C_4 alkyl) amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

R^{138} is selected from:

hydrogen;

straight or branched C_1 –C_4 alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from

halo, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

C_3 –C_8 cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are indepently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

C_4 –C_8 cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, □ydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-[C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)]amino, N-[(C_1 –C_4 alkyl)sulfony]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbomoyl, [N-(C_1 –C_4 alky)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl; and

heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{20};

R^{139} and R^{140} are independently selected from:

hydrogen;

halo;

C_1 –C_4 alkyl;

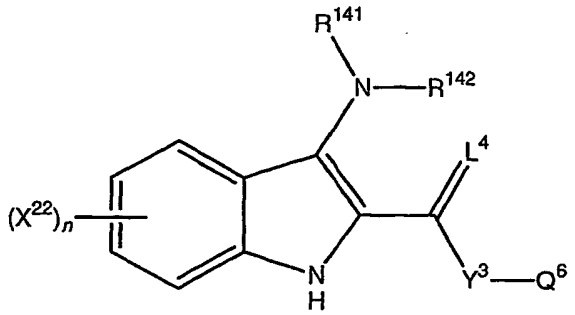
phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a C_3 –C_7 cycloalkyl ring;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

[000104] Compounds that may be employed as a Cox-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



XXVII

and the pharmaceutically acceptable salts thereof, wherein:

L^4 is oxygen or sulfur;

Y^3 is a direct bond or C_1 –C_4 alkylidene;

Q^6 is:

(a) C_1 –C_6 alkyl or halosubstituted C_1 –C_6 alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkoxy, amino and mono- or di-(C_1 –C_4 alkyl)amino,

(b) C_3 –C_7 cycloalkyl optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkyl and C_1 –C_4 alkoxy,

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$ and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_1 –C_4 alkyl, CF_3, hydroxyl, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substitutents independently selected from:

(d-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, C_1 –C_4 alkyl-OH, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF_3, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, OCF_3, SR^{143}, $SO_2 CH_3$, $SO_2 NH_2$, amino, C_{1-4} alkylamino and $NHSO_2 R^{143}$;

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R^{141} is hydrogen or C_1 –C_6 alkyl optionally substituted with a substituent selected independently from hydroxyl, OR^{143}, nitro, amino, mono- or di-(

C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, CONH(C_1 –C_4 alkyl) and CON(C_1 –C_4 alkyl)$_2$;

R^{142} is:

(a) hydrogen,

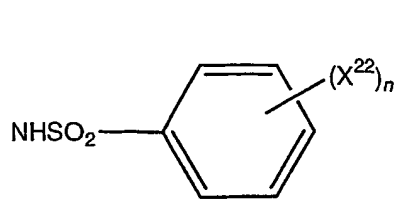
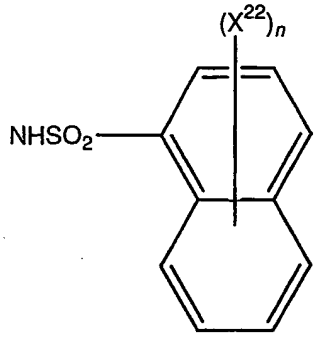
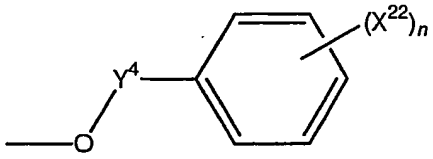
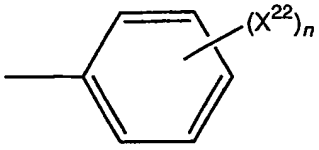
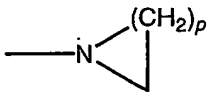
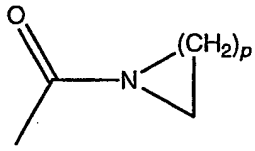
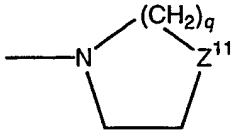
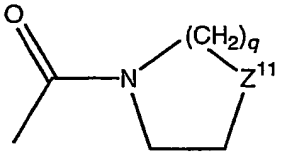
(b) C_1 –C_4 alkyl,

(c) C(O)R^{145},

wherein R^{145} is selected from:

(c-1) C_1 –C_{22} alkyl or C_2 –C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:

(c-1-1) halo, hydroxyl, OR^{143}, $S(O)_m$ R^{143}, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2$ R^{143}, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, CONH(C_1 –C_4 alkyl), CON(C_1 –C_4 alkyl)$_2$, OC(O)R^{143}, thienyl, naphthyl and groups of the following formulas:

(c-2) C_1 –C_{22} alkyl or C_2 –C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3) –Y^5—C_3 –C_7 cycloalkyl or –Y^5—C_3 –C_7 cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C_1 –C_4 alkyl, hydroxyl, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

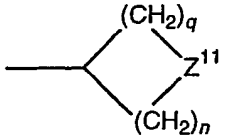
(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, halosubstituted C_1 –C_8 alkyl, halosubstituted C_1 –C_8 alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_1$ –C_4 alkyl), $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, C_1 –C_4 alkylamino, di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, OCH_3, CF_3, OCF_3, CN, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl) and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, CO_2 H and CO_2 (C_1 –C_4 alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstitutued C_1 –C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, nitro, halosubstitutued C_1 –C_4 alkyl, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkylOR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl) or $CON(C_1$ –C_4 alkyl)$_2$;

R^{143} is C_1 –C_4 alkyl or halosubstituted C_1 –C_4 alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{144} ; and

R^{144} is hydrogen, C_1 –C_6 alkyl, halosubstitutued C_1 –C_4 alkyl or –Y^5-phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, CF_3, OCF_3, CN and nitro;

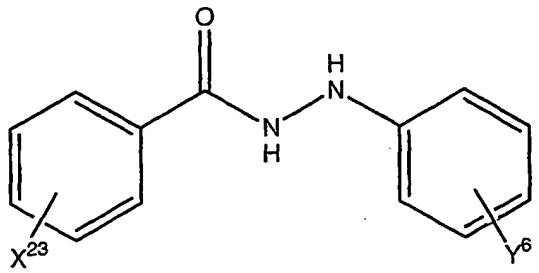
with the proviso that a group of formula –Y^5—Q is not methyl or ethyl when X^{22} is hydrogen;

L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl.

[000105] Aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869 can serve as Cox-2 selective inhibitors of the present invention. Such aryl phenylhydrazides have the formula shown below in formula **XXVIII**:



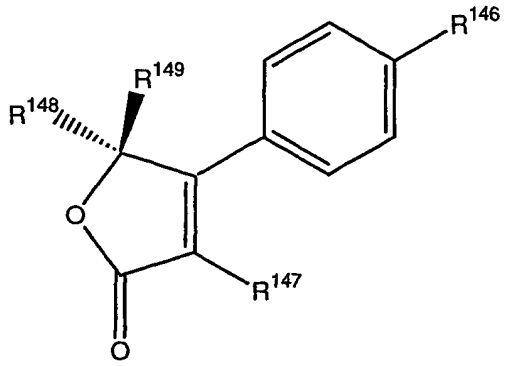
XXVIII

wherein:

X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino, hydroxy, methoxy and methylsulfonyl;

or a pharmaceutically acceptable salt thereof,.

[000106] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula **XXIX**:



XXIX

or a pharmaceutical salt thereof, wherein:

R^{146} is selected from the group consisting of SCH_3, —$S(O)_2$ CH_3 and — $S(O)_2$ NH_2 ;

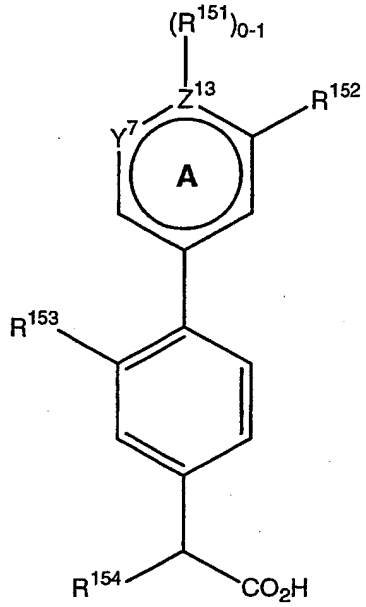
R^{147} is selected from the group consisting of OR^{150}, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

[000107] Materials that can serve as a Cox-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX**:



XXX

or a pharmaceutically acceptable salt, ester or tautomer thereof, wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an

energetically stable configuration planar with ring A to within about 15 degrees;

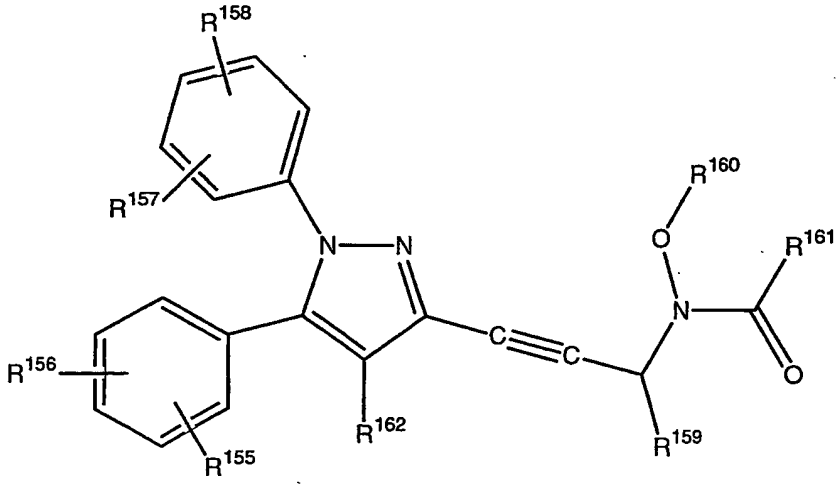
said ring D further being substituted with 1 R^a group selected from the group consisting of: C_1 –C_2 alkyl, —OC_1 –C_2 alkyl, —NHC_1 –C_2 alkyl, —$N(C_1$ –C_2 alkyl$)_2$, —C(O) C_1 –C_2 alkyl, —S—C_1 –C_2 alkyl and —C(S) C_1 –C_2 alkyl;

Y^7 represents N, CH or C—OC_1 –C_3 alkyl, and when Z^{13} is N, Y^7 can also represent a carbonyl group;

R^{153} represents H, Br, Cl or F; and

R^{154} represents H or CH_3.

[000108] Compounds useful as Cox-2 selective inhibitors of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI**:



XXXI

wherein:

R^{155}, R^{156}, R^{157}, and R^{158} are independently selected from the groups consisting of hydrogen, C_1 –C_5 alkyl, C_1 –C_5 alkoxy, phenyl, halo, hydroxyl, C_1 –C_5 alkylsulfonyl, C_1 –C_5 alkylthio, trihaloC_1 –C_5 alkyl, amino, nitro and 2-quinolinylmethoxy;

R^{159} is hydrogen, C_1 –C_5 alkyl, trihaloC_1 –C_5 alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;

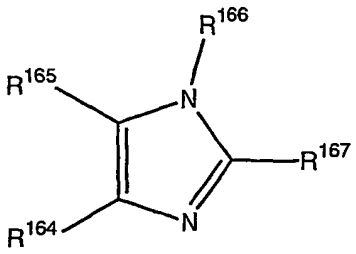
R^{160} is hydrogen, C_1 –C_5 alkyl, phenyl C_1 –C_5 alkyl, substituted phenyl C_1 –C_5 alkyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro, or R^{160} is C_1 –C_5 alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro;

R^{161} is C_1 –C_{10} alkyl, substituted C_1 –C_{10} alkyl where the substituents are halogen, trihaloC_1 –C_5 alkyl, C_1 –C_5 alkoxy, carboxy, C_1 –C_5 alkoxycarbonyl, amino, C_1 –C_5 alkylamino, diC_1 –C_5 alkylamino, diC_1 –C_5 alkylaminoC_1 –C_5 alkylamino, C_1 –C_5 alkylaminoC_1 –C_5 alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C_1 –C_5 alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C_1 –C_5 alkyl, halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or

R^{161} is NR^{163} R^{164} where R^{163} and R^{164} are independently selected from hydrogen and $C_{1\text{-}5}$ alkyl or R^{163} and R^{164} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_1 –C_5 alkyl; R^{162} is hydrogen, C_1 –C_5 alkyl, nitro, amino, and halogen;

and pharmaceutically acceptable salts thereof.

[000109] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-substituted imidazoles that are described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula **XXXII**:



XXXII

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl and halogen, or

substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{166} is hydrogen, 2-(trimethylsilyl)ethoxymethyl), C_1 –C_5 alkoxycarbonyl, aryloxycarbonyl, arylC_1 –C_5 alkyloxycarbonyl, arylC_1 –C_5 alkyl, phthalimidoC_1 –C_5 alkyl, aminoC_1 –C_5 alkyl, diaminoC_1 –C_5 alkyl, succinimidoC_1 –C_5 alkyl, C_1 –C_5 alkylcarbonyl, arylcarbonyl, C_1 –C_5 alkylcarbonylC_1 –C_5 alkyl, aryloxycarbonylC_1 –C_5 alkyl, heteroarylC_1 –C_5 alkyl where the heteroaryl contains 5 to 6 ring atoms, or

substituted arylC_1 –C_5 alkyl,

wherein the aryl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, C_1 –C_5 alkoxy, halogen, amino, C_1 –C_5 alkylamino, and diC_1 –C_5 alkylamino;

R^{167} is $(A^{11})_n$–$(CH^{165})_q$–X^{24} wherein:

A^{11} is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X^{24} is selected from the group consisting of hydrogen, hydroxyl, halogen, vinyl, ethynyl, C_1 –C_5 alkyl, C_3 –C_7 cycloalkyl, C_1 –C_5 alkoxy, phenoxy, phenyl, arylC_1 –C_5 alkyl, amino, C_1 –C_5 alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylthio, C_1 –C_5 alkylsulfonyl, phenylsulfonyl,

substituted sulfonamido,

wherein the sulfonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, araC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine,

substituted C_1 –C_5 alkyl,

wherein the substituents are selected from the group consisting of one or more C_1 –C_5 alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted phenoxy,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 – C_5 alkoxy,

substituted C_1 –C_5 alkoxy,

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,

substituted arylC_1 –C_5 alkyl,

wherein the alkyl substituent is hydroxyl,

substituted arylC_1 –C_5 alkyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 – C_5 alkoxy,

substituted amido,

wherein the carbonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, arylC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted C_1 –C_5 alkylthio,

wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,

substituted C_1 –C_5 alkylsulfonyl,

wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,

substituted phenylsulfonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_1 –C_5 alkoxy and trifluoromethyl,

with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

if A^{11} is sulfur and q is 1, then X^{24} cannot be C_1 –C_2 alkyl;

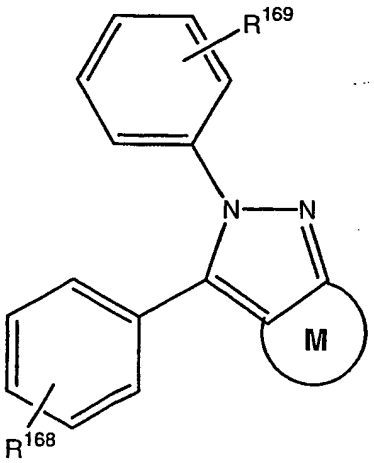
if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl;

if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not 2-(trimethylsilyl)ethoxymethyl;

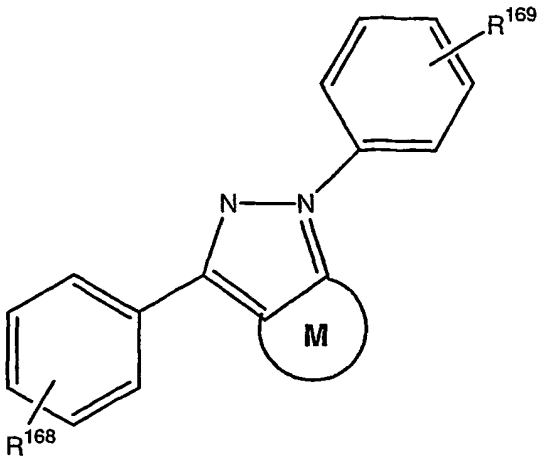
if n is 0 and q is 0, then X^{24} cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

[000110] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:



XXXIII

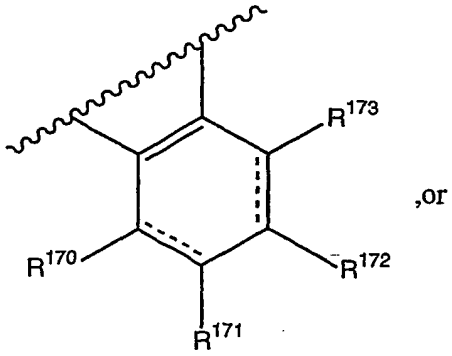


XXXIV

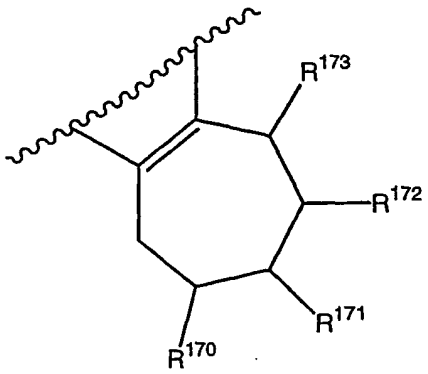
wherein:

R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, nitro, amino, □ydroxyl, trifluoro, —S(C_1-C_6)alkyl, —SO(C_1-C_6)alkyl and —SO_2 (C_1-C_6)alkyl; and

the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



,or



wherein:

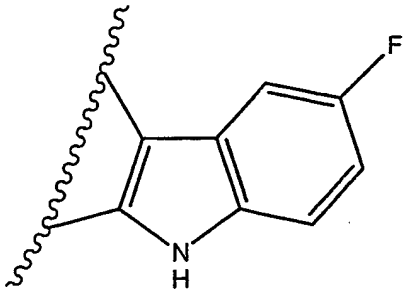
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxyl and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of —$OCOCH_2$ —, —$ONH(CH_3)COCH_2$ —, —OCOCH= and —O—;

R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy, =NOH, —NR^{174} R^{175}, —OCH_3, —OCH_2 CH_3, —OSO_2 $NHCO_2$ CH_3, =$CHCO_2$ CH_2 CH_3, —CH_2 CO_2 H, —CH_2 CO_2 CH_3, —CH_2 CO_2 CH_2 CH_3, —CH_2 $CON(CH_3)_2$, —CH_2 CO_2 $NHCH_3$, —$CHCHCO_2$ CH_2 CH_3, —$OCON(CH_3)OH$, —$C(COCH_3)_2$, di(C_1 –C_6)alkyl and di(C_1 –C_6)alkoxy;

R^{173} is selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxyl, amino, (C_1 –C_6)alkyl and (C_1 –C_6)alkoxy;

or R^{172} and R^{173} taken together form a moiety selected from the group consisting of —O—and



R^{174} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$ and (C_1 –C_6)alkyl; and

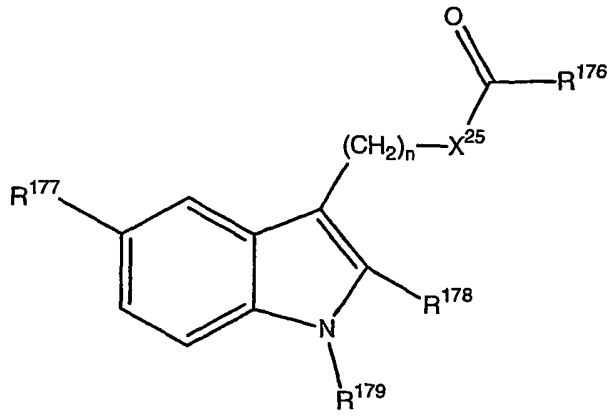
R^{175} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$, (C_1 –C_6)alkyl, —$CONH_2$ and —SO_2 CH_3 ;

with the proviso that

if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

[000111] Esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890 can serve as Cox-2 selective inhibitors of the present invention. Such compounds have the general formula shown below in formula **XXXV**:



XXXV

wherein:

R^{176} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_1 –C_6 hydroxyalkyl, branched C_1 –C_6 hydroxyalkyl, hydroxyl substituted C_4 –C_8 aryl, primary, secondary or tertiary C_1 –C_6 alkylamino, primary, secondary or tertiary branched C_1 –C_6 alkylamino, primary, secondary or tertiary C_4 –C_8 arylamino, C_1 –C_6 alkylcarboxylic acid, branched C_1 –C_6 alkylcarboxylic acid, C_1 –C_6 alkylester, branched C_1 –C_6 alkylester, C_4 –C_8 aryl, C_4 –C_8 arylcarboxylic acid, C_4 –C_8 arylester, C_4 –C_8 aryl substituted C_1 –C_6 alkyl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R^{177} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_4 –C_8 aryl, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, C_1 –C_6 branched alkoxy, C_4 –C_8 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

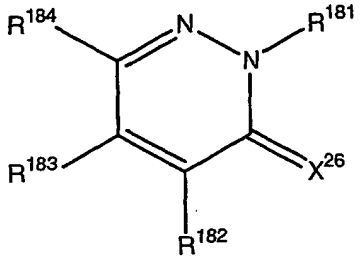
R^{178} is hydrogen, C_1 –C_6 alkyl or C_1 –C_6 branched alkyl;

R^{179} is C_1 –C_6 alkyl, C_4 –C_8 aroyl, C_4 –C_8 aryl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C_4 –C_8 aroyl, or alkyl-substituted C_4 –C_8 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

n is 1, 2, 3, or 4; and

X^{25} is O, NH, or N—R^{180}, where R^{180} is C_1 –C_6 or C_1 –C_6 branched alkyl.

[000112] Materials that can serve as a Cox-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI**:



XXXVI

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X^{26} is selected from the group consisting of O, S, —NR^{185}, —NOR^a, and –$NNR^b R^c$;

R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

R^a, R^b, and R^c are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl,

cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, $-(CH_2)_n C(O)R^{186}$, $-(CH_2)_n CH(OH)R^{186}$, $-(CH_2)_n C(NOR^d)R^{186}$, $-(CH_2)_n CH(NOR^d)R^{186}$, $-(CH_2)_n CH(NR^d R^e)R^{186}$, $-R^{187} R^{188}$, $-(CH_2)_n C\equiv CR^{188}$, $-(CH_2)_n [CH(CX^{26'}{}_3)]_m (CH_2)_p R^{188}$, $-(CH_2)_n (CX^{26'}{}_2)_m (CH_2)_p R^{188}$, and $-(CH_2)_n (CHX^{26'})_m (CH_2)_m R^{188}$;

R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

$X^{26'}$ is halogen;

m is an integer from 0-5;

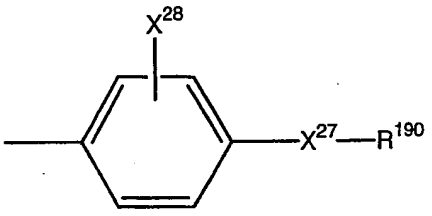
n is an integer from 0-10;

p is an integer from 0-10;

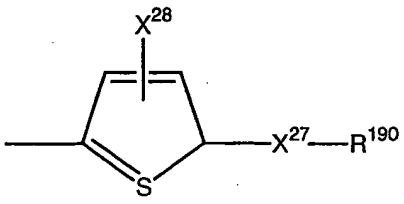
R^{182}, R^{183}, and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8, and Z^{14};

provided that one of R^{182}, R^{183}, or R^{184} must be Z^{14}, and further provided that only one of R^{182}, R^{183}, or R^{184} is Z^{14};

Z^{14} is selected from the group consisting of:



and



X^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, $S(O)$, $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193}\ R^{194})$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, —$NHNH_2$, and —$NCHN(R^{191})R^{192}$;

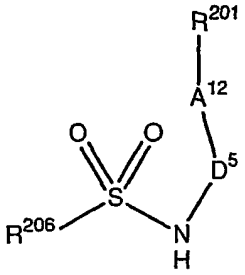
R^{191}, R^{192}, R^{193}, and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

Y^8 is selected from the group consisting of –OR^{195}, —SR^{195}, —$C(R^{197})(R^{198})R^{195}$, —$C(O)R^{195}$, —$C(O)OR^{195}$, —$N(R^{197})C(O)R^{195}$, —$NC(R^{197})R^{195}$, and —$N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and $NR^{199}\ R^{200}$; and

R^{197}, R^{198}, R^{199}, and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

[000113] Benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948 are useful as Cox-2 selective inhibitors of the present invention. Such benzosulphonamide derivatives have the formula shown below in formula **XXXVII**:



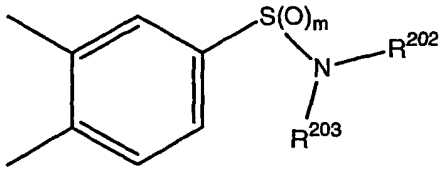
XXXVII

wherein:

A^{12} denotes oxygen, sulphur or NH;

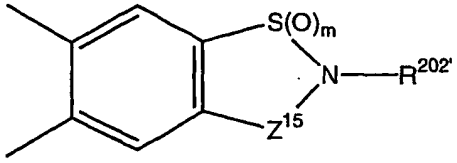
R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 or alkoxy;

D^5 denotes a group of formula **XXXVIII** or **XXXIX**:



XXXVIII

or



XXXIX

R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n-X^{29}$; or

R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one

or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n-X^{29}$, $R^{202,}$ denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n-X^{29}$,

wherein:

X^{29} denotes halogen, NO_2, $—OR^{204}$, $—COR^{204}$, $—CO_2R^{204}$, $—OCO_2R^{204}$, —CN, $—CONR^{204}OR^{205}$, $—CONR^{204}R^{205}$, $—SR^{204}$, $—S(O)R^{204}$, $—S(O)_2R^{204}$, $—NR^{204}R^{205}$, $—NHC(O)R^{204}$, $—NHS(O)_2R^{204}$;

Z^{15} denotes $—CH_2—$, $—CH_2—CH_2—$, $—CH_2—CH_2—CH_2—$, $—CH_2—CH=CH—$, $—CH=CH—CH_2—$, $—CH_2—CO—$, $—CO—CH_2—$, —NHCO—, —CONH—, $—NHCH_2—$, $—CH_2NH—$, —N=CH—, —NHCH—, $—CH_2—CH_2—NH—$, —CH=CH—, $>N—R^{203}$, >C=O, $>S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

n is an integer from 0 to 6;

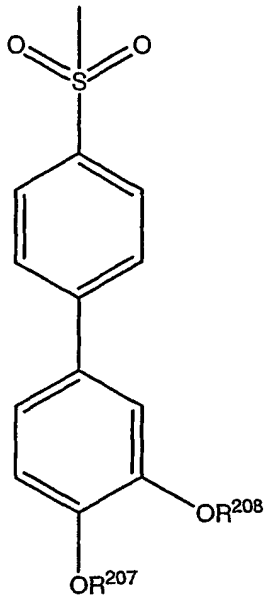
R^{206} is a straight-chained or branched C_1-C_4 alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3; and

m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3;

and the pharmaceutically acceptable salts thereof.

[000114] Materials that can serve as Cox-2 selective inhibitors of the present invention include methanesulfonyl-biphenyl derivatives that are described in U.S. Patent No. 6,583,321. Such methanesulfonyl-biphenyl derivatives have the formula shown below in formula **XXXX**:



XXXX

wherein:

R^{207} and R^{208} are respectively a hydrogen;

C_1 –C_4-alkyl substituted or not substituted by halogens;

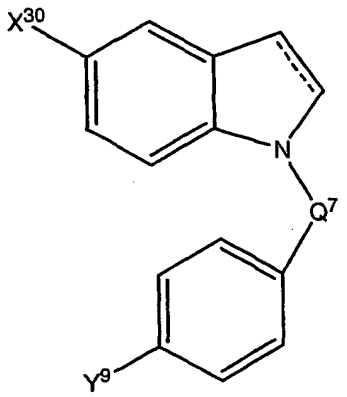
C_3 –C_7-cycloalkyl;

C_1 –C_5-alkyl containing 1-3 ether bonds and/or an aryl substitute;

substituted or not substituted phenyl;

or substituted or not substituted five or six ring-cycled heteroaryl containing more than one hetero atoms selected from a group consisting of nitrogen, sulfur, and oxygen (wherein phenyl or heteroaryl can be one- or multi-substituted by a substituent selected from a group consisting of hydrogen, methyl, ethyl, and isopropyl).

[000115] Cox-2 selective inhibitors such as 1H-indole derivatives described in U.S. Patent No. 6,599,929 are useful in the present invention. Such 1H-indole derivatives have the formula shown below in formula **XXXXI**:



XXXXI

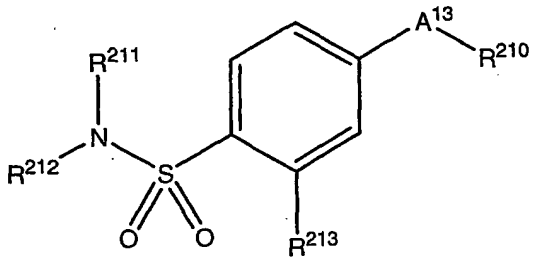
wherein:

X^{30} is $-NHSO_2R^{209}$ wherein R^{209} represents hydrogen or C_1 $-C_3$–alkyl;

Y^9 is hydrogen, halogen, C_1 $-C_3$–alkyl substituted or not substituted by halogen, NO_2, NH_2, OH, OMe, CO_2H, or CN; and

Q^7 is C=O, C=S, or CH_2.

[000116]. Compounds that are useful as Cox-2 selective inhibitors of the present invention include prodrugs of Cox-2 inhibitors that are described in U.S. Patent Nos. 6,436,967 and 6,613,790. Such prodrugs of Cox-2 inhibitors have the formula shown below in formula **XXXXII**:



XXXXII

wherein:

A^{13} is a ring substituent selected from partially unsaturated heterocyclic, heteroaryl, cycloalkenyl and aryl, wherein A^{13} is unsubstituted or substituted with one or more radicals selected from alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, cycloalkylalkyl, alkenyl, alkynyl, heterocycloxy, alkylthio, cycloalkyl, aryl,

heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, araalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, -arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl;

R^{210} is selected from heterocyclyl, cycloalkyl, cycloalkenyl, and aryl, wherein R^{210} is unsubstituted or substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} is selected from hydrido and alkoxycarbonylalkyl;

R^{212} is selected from alkyl, carboxyalkyl, acyl, alkoxycarbonyl, heteroarylcarbonyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylcarbonyl, amino acid residue, and alkylcarbonylaminoalkylcarbonyl;

provided A^{13} is not tetrazolium, or pyridinium; and further provided A^{13} is not indanone when R^{212} is alkyl or carboxyalkyl; further provided A^{13} is not thienyl, when R^{210} is 4-fluorophenyl, when R^{211} is hydrido, and when R^{212} is methyl or acyl; and

R^{213} is hydrido;

or a pharmaceutically-acceptable salt thereof.

[000117] Specific non-limiting examples of substituted sulfonamide prodrugs of Cox-2 inhibitors disclosed in U.S. Patent No. 6,436,967 that are useful in the present invention include:

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]propanamide;

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]butanamide;

N-[[4-[1,5-dimethyl)-3-phenyl-1H-pyrazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(3-chloro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
2-methyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]benzamide;
2,2-dimethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]pentanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]hexanamide;
3-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide ;
2-ethoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H pyrazol-1-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;

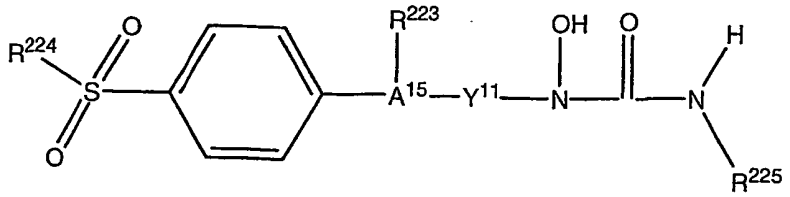
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-6-fluoro-1,5-dihydro-7-methoxy-[2]benzothiopyrano [4,3-c]pyrazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[6-fluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-methyl-4-phenyloxazol-5-yl)phenyl]sulfonyl]acetamide;
methyl[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]oxoacetate;
2-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]formamide;
1,1-dimethylethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-[[.sup.4 -(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine;
2-amino-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
2-(acetylamino)-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
methyl 4-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-4-oxobutanoate;
methyl N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-acetyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine, ethyl ester;
N-[[4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]sulfonyl]acetamide;
methyl 3-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-3-oxopropanoate;

4-[5-(3-bromo-5-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)oxazol-4-yl]-N-methylbenezenesulfonamide;
N-(1,1-dimethylethyl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-methylbenzenesulfonamide;
N-methyl-4-(5-methyl-3-phenylisoxazol-4-yl)benezenesulfonamide;
N-[[4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide:
N-[[4-[5-(acetoxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl)phenyl]sulfonyl]acetamide;
4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]-N-methylbenzenesulfonamide;
N-[[4-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl]phenyl]sulfonyl]propanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-trifluoromethylimidazol-1-yl]phenyl]sulfonyl]propanamide;
4-[2-(4-fluorophenyl)cyclopenten-1-yl]-N-methylbenezenesulfonamide; and
N-[[4-(3-phenyl-2,3-dihydro-2-oxofuran-4-yl)phenyl]sulfonyl]propanamide.

[000118] Those prodrugs disclosed in U.S. Patent No. 6,613,790 have the general formula shown above in formula **XXXXII** wherein:

A^{13} is a pyrazole group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, intro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, alkenyl, alkynyl, alkylthio, alkylthioalkyl, alkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkylsutfinyl, alkylsulfonyl, aminosulfonyl, and alkylaminosulfonyl;

R^{210} is a phenyl group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl,



XXXXVI

[000123] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is selected from lower alkenylene and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000124] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 may also have the formula shown above in formula **XXXXVI**, wherein:

A^{15} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkylene, lower alkenylene and lower alkynylene;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido, lower alkyl;

or a pharmaceutically-acceptable salt thereof.

[000125] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is a ring substiuent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isochiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A^{14} is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is lower alkylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is otionallv substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000126] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 may also have the formula shown above in formula **XXXXVI**, wherein:

A^{15} is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isothiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarboryl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitto, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000127] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is ethylene, isopropylene, propylene, butylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position

with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000128] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 may also have the formula shown above in formula **XXXXV**, wherein:

A^{15} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

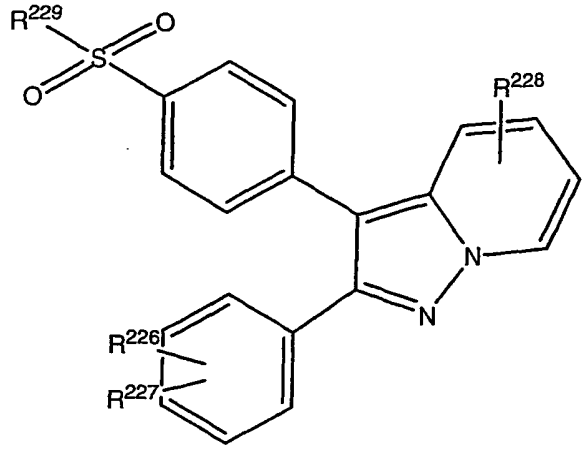
Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000129] Compounds that are useful as Cox-2 selective inhibitors of the present invention include pyrazolopyridine compounds that are described in U.S. Patent No. 6,498,166. Such pyrazolopyridine compounds have the formula shown below in formula **XXXXVII**:



XXXXVII

wherein:

R^{226} and R^{227} are independently selected from the group consisting of H, halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms;

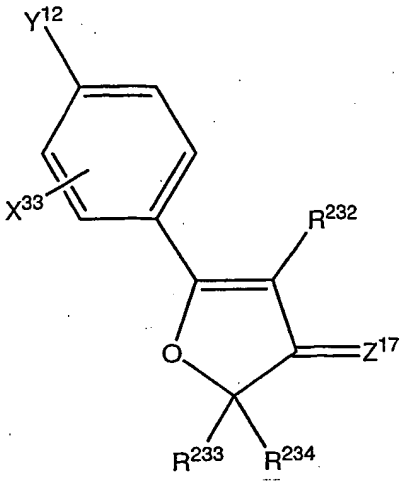
R^{228} is halogen, CN, CON R^{230} R^{231}, CO_2 H, CO_2 C_1 –C_6 alkyl, or $NHSO_2R^{230}$;

R^{229} is C_1 –C_6 alkyl or NH_2 ; and

R^{225} and R^{225} are independently selected from the group consisting of H, C_1 –C_6 alkyl, phenyl, phenyl substituted by one or more atoms or groups selected from the group consisting of halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms,

or a pharmaceutically acceptable salt, solvate, ester, or salt or solvate of such ester thereof.

[000130] Materials that are useful as Cox-2 selective inhibitors of the present invention include 4,5-diaryl-3(2H)-furanone derivatives that are described in U.S. Patent No. 6,492,416. Such 4,5-diaryl-3(2H)-furanone derivatives have the formula shown below in formula **XXXXVIII**:



XXXXVIII

wherein:

X^{33} represents halo, hydrido, or alkyl;

Y^{12} represents alkylsulfonyl, aminosulfonyl, alkylsulfinyl, (N-acylamino)-sulfonyl, (N-alkylamino)sulfonyl, or alkylthio;

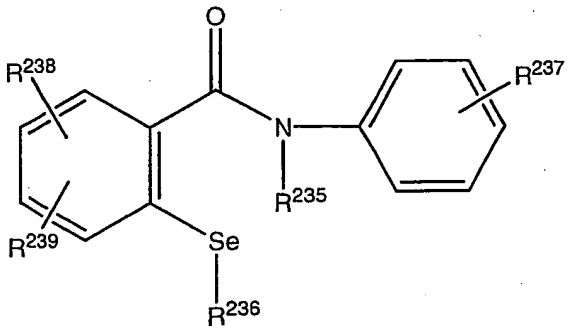
Z^{17} represents oxygen or sulfur atom;

R^{233} and R^{234} are selected independently from lower alkyl radicals;

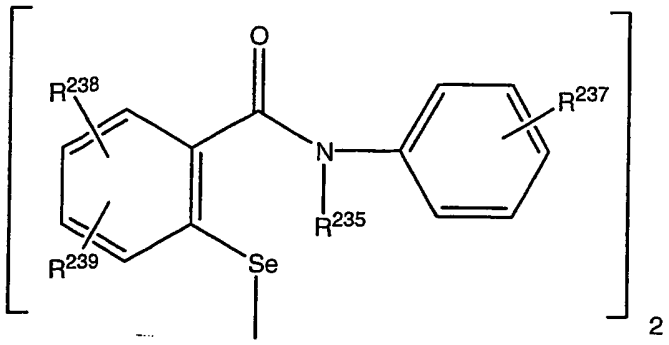
and R^{232} represents a substituted or non-substituted aromatic group of 5 to 10 atoms;

or a pharmaceutically-acceptable salt thereof.

[000131] Cox-2 selective inhibitors that can be used in the present invention include 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives that are described in U.S. Patent No. 6,492,416. Such 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives have the formulas shown below in formulas **XXXXIX** or **XXXXIX'**:



XXXXIX



XXXXIX'

wherein:

R^{235} is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

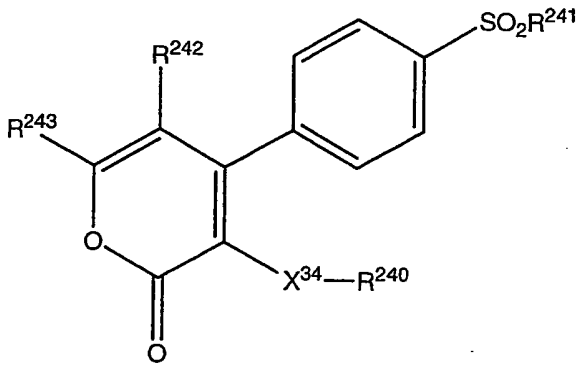
R^{236} is a hydrogen atom, a hydroxyl group, an organothiol group that is bound to the selenium atom by its sulfur atom, or R^{235} and R^{236} are joined to each other by a single bond;

R^{237} is a hydrogen atom, a halogen atom, an alkyl group having 1-3 carbon atoms, an alkoxyl group having 1-3 carbon atoms, a trifluoromethyl group, or a nitro group;

R^{238} and R^{239} are identical to or different from each other, and each is a hydrogen atom, a halogen atom, an alkoxyl group having 1-4 carbon atoms, a trifluoromethyl group, or R^{238} and R^{239} are joined to each other to form a methylenedioxy group,

a salt thereof, or a hydrate thereof.

[000132] Pyrones such as those disclosed in U.S. Patent No. 6,465,509 are also useful as Cox-2 inhibitors of the present invention. These pyrone compounds have the general formula shown below in formula **XXXXX:**



XXXXX

wherein:

X^{34} is selected from the group consisting of:

(a) a bond,

(b) --$(CH_2)_m$ --, wherein m 1 or 2,

(c) --C(O)--,

(d) --O--,

(e) --S--, and

(f) --$N(R^{244})$--;

R^{240} is selected from the group consisting of:

(a) C_1 –C_{10} alkyl, optionally substituted with 1-3 substituents independently selected from the group consisting of: hydroxy, halo, C_1 –C_{10} alkoxy, C_1 – C_{10} alkylthio, and CN,

(b) phenyl or naphthyl, and

(c) heteroaryl, which is comprised of a monocyclic aromatic ring of 5 atoms having one hetero atom which is S, O or N, and optionally 1, 2, or 3 additional N atoms; or

a monocyclic ring of 6 atoms having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein groups (b) and (c) above are each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, C_1 –C_{10} alkoxy, C_1 –C_{10} alkylthio, CN, C_1 –C_{10} alkyl, optionally substituted to its maximum with halo, and N_3 ;

R^{241} is selected from the group consisting of

(a) C_1 –C_6 alkyl, optionally substituted to its maximum with halo,

(b) NH_2, and

(c) NHC(O)C_1 –C_{10} alkyl, optionally substituted to its maximum with halo;

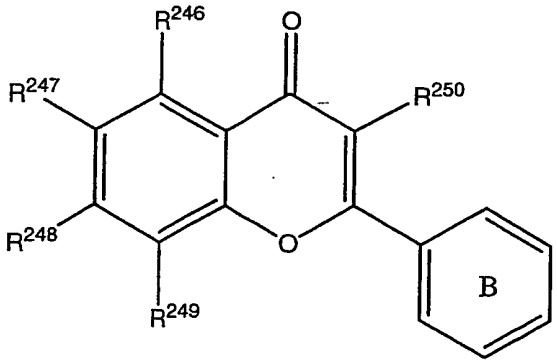
R^{242} and R^{243} are each independently selected from the group consisting of: hydrogen, halo, and C_1 –C_6 alkyl, optionally substituted to its maximum with halo; and

R^{244} is selected from the group consisting of: hydrogen and C_1 –C_6 alkyl, optionally substituted to its maximum with halo.

[000133] Examples of pyrone compounds that are useful as Cox-2 selective inhibitors of the present invention include, but are not limited to:

4-(4-Methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
3-(4-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
3-(3-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Difluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Fluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenylthio-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenoxy-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-pyridin-3-yl-pyran-2-one,
3-Isopropylthio-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl)-3-phenylthio-6-trifluoromethyl-pyran-2-one,
3-Isopropylthio-4-(4-methylsulfonyl)phenyl-6-trifluoromethyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl-3-phenyl-6-(2,2,2-trifluoroethyl)-pyran-2-one, and
3-(3-Hydroxy-3-methylbutyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one.

[000134] Organically synthesized or purified from plant sources, free-B-ring flavanoids such as those described in U.S. Published Application No. 2003/0165588, are useful as Cox-2 selective inhibitors of the present invention. Such free-B-ring flavanoids have the general structure shown in formula **XXXXXI**:

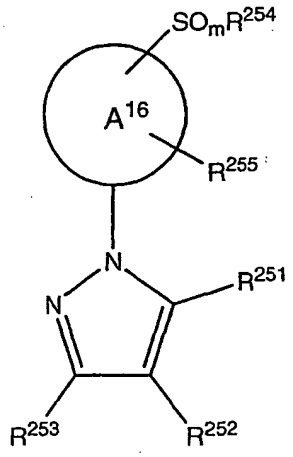


XXXXXI

wherein:

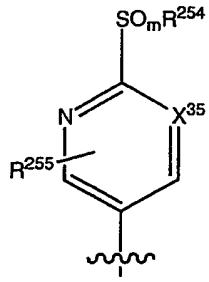
R^{246}, R^{247}, R^{248}, R^{249}, and R^{250} are independently selected from the group consisting of: --H, --OH, --SH, --OR, --SR, $--NH_2$, $--NHR^{245}$, $--N(R^{245})_2$, $--N(R^{245})_3{}^{+}X^{35-}$, a carbon, oxygen, nitrogen or sulfur, glycoside of a single or a combination of multiple sugars including, aldopentoses, methyl-aldopentose, aldohexoses, ketohexose and their chemical derivatives thereof; wherein R^{245} is an alkyl group having between 1-10 carbon atoms; and X^{35} is selected from the group of pharmaceutically acceptable counter anions including, hydroxyl, chloride, iodide, sulfate, phosphate, acetate, fluoride and carbonate.

[000135] Heterocyclo-alkylsulfonyl pyrazoles such as those described in European Patent Application No. EP 1312367 are useful as Cox-2 selective inhibitors of the present invention. Such heterocyclo-alkylsulfonyl pyrazoles have the general formula shown below in formula **XXXXXII**:



XXXXXII

or a pharmaceutically acceptable salt thereof, wherein:
the ring of the formula (R^{255})-A-(SO_mR^{254}) is selected from the group consisting of:



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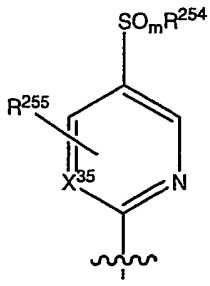

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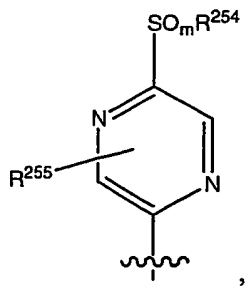

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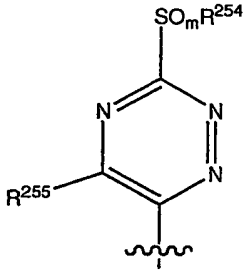

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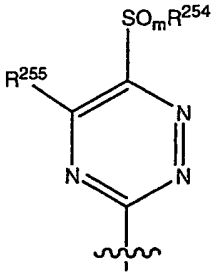
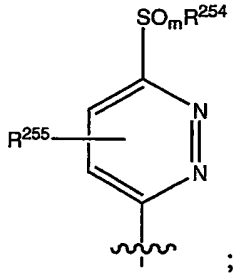


, and


;

m is 0, 1 or 2;

X^{35} is $>CR^{255}$ or >N;

R^{251} is a radical selected from the group consisting of H, NO_2, CN, (C_1 – C_6)alkyl, (C_1 –C_6)alkyl-SO_2-, (C_6 –C_{10})aryl-SO_2-, H-(C=O)-, (C_1 –C_6)alkyl-(C=O)-, (C_1 –C_6)alkyl-)-(C=O)-, (C_1 –C_9)heteroaryl-(C=O)-, (C_1 – C_9)heterocyclyl-(C=O)-, H_2N-(C=O)-, (C_1 –C_6)alkyl-NH-(C=O)-, [(C_1 – C_6)alkyl]$_2$-N-(C=O)-, [(C_6 –C_{10})aryl]$_2$-NH-(C=O)-, [(C_1 –C_6)alkyl]-[((C_6 – C_{10})aryl-N]-(C=O)-, HO-NH-(C=O)-, and (C_1 –C_6)alkyl-O-NH-(C=O)-;

R^{252} is a radical selected from the group consisting of H, -NO_2, -CN, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_1-C_9)heteroaryl, (C_1-C_9)heterocyclyl, (C_1-C_6)alkyl-O-, (C_3-C_7)cycloalkyl-O-, (C_6-C_{10})aryl-O-, (C_1 -C_9)heteroaryl-O-, (C_6 -C_9)heterocyclyl-O-, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_3-C_7)cycloalkyl-(C=O)-, (C_6-C_{10})aryl-(C=O)-, (C_1-C_9)heteroaryl-(C=O)-, (C_1-C_9)heterocyclyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_7)cycloalkyl-O-(C=O)-, (C_6-C_{10})aryl-O-(C=O)-, (C_1-C_9)heteroaryl-O-(C=O)-, (C_1-C_9)heterocyclyl-O-(C=O)-, (C_1-C_6)alkyl-(C=O)-O-, (C_3-C_7)cycloalkyl-(C=O)-O-, (C_6-C_{10})aryl-(C=O)-O-, (C_1-C_9)heteroaryl-(C=O)-O-, (C_1-C_9)heterocyclyl-(C=O)-O-, (C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_7)cycloalkyl-(C=0)-NH-, (C_6-C_{10}aryl-(C=O)-NH-. (C_1-C_9)heteroaryl-(C=O)-NH-, (C_1-

C_9)heterocyclyl-(C=O)-NH-, (C_1-C_6)alkyl-O-(C=O)-NH-, (C_1-C_6)alkyl-NH, [(C_1-C_6)alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-. [(C_3-C_7)cycloalkyl]$_2$-N-, [(C_6-C_{10})aryl]-NH-, [(C_6-C_{10})aryl]$_2$-N-, [(C_1 –C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, [(C_1 - C_9)heteroaryl]-NH-, [(C_1-C_9)heteroaryl]$_2$-N-, [(C_1-C_9)heterocycly]-NH-, [(C_1-C_9)heterocyclyl]$_2$-N-, H_2N-(C=O)-, HO-NH-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, [(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_3-C_7)cycloalkyl]-NH-(C=O)-, [(C_3-C_7)cycloalkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_6-C_{10}aryl]$_2$-N-(C=O)-, [(C_1-C $_6$)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, [(C_1-C_9)heteroaryl]-NH-(C=O)-, [(C_1-C_9)heferoaryl]$_2$-N-(O=O)-, [(C_1-C_9)heterocyclyl]-NH-(C=O)-, (C_1–C_6)alkyl-S- and (C_1-C_6)alkyl optionally substituted by one -OH substituent or by one to four fluoro substituents;

R^{253} is a saturated (3- to 4-membered)-heterocyclyl ring radical; or a saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical orsaid saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may optionally contain one to four ring heteroatoms independently selected lrom the groups consisting of -N=, -NH-, -O-. and -S-;

wherein said saturated (3- to 4-membered)-heterooyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-nembered)-heterocyclyl ring radical; may optionally be substituted on any ring carbon atom by one to three substituents per ring independently selected from the group consisting of halo, -OH, -CN, -NO_2, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)hetorocyclyl, (C_1 –C_6)alkyl-O-, H-(C=0)-, (C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, -NH_2, (C_1-C_6)alkyl-NH-, [(C_1-C_6) alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-, (C_6-C_{10})aryl-NH-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, (C_1-C_9)heteroaryl-NH-, H_2N-(C=O)-[(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-HN-, (C_1-C_6)alkyl-(C=O)-[(C_1-C_6)alkyl-N]-, -SH, (C_1-C_6)alkyl-S-,

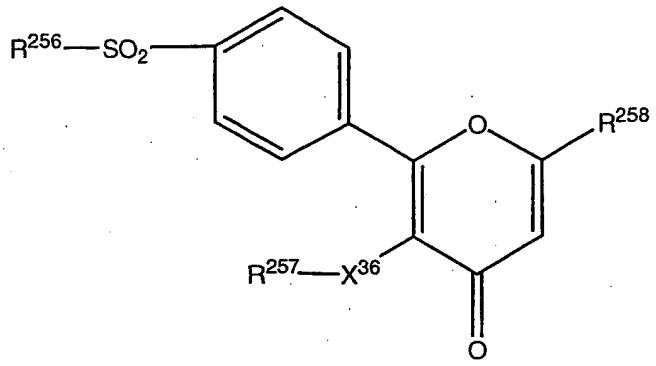
$(C_1$-$C_6)$alkyl-(S=0)-, $(C_1$-$C_6)$alkyl-SO_2- and $(C_1$-$C_6)$alkyl optionally substituted with one to fourfluoro moieties;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may also optionally be substituted on any ring nitrogen atom by one to three substituents per ring independently selected from the group consisting of $(C_3$-$C_7)$cyoloalkyl, $(C_6$-$C_{10})$aryl, $(C_2$-$C_9)$heterocyclyl, H-(C=O)-, $(C_1$-$C_6)$alkyl-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, H_2N-(C=O)-, [$(C_1$-$C_6)$alkyl]-NH-(C=O)-, [$(C_1$-$C_6)$alkyl]$_2$-N-(C=O)-, [$(C_6$-$C_{10})$aryl]-NH-(C=O)-, [$(C_1$-$C_6)$alkyl]-[($(C_6$-$C_{10})$aryl)-N]-(C=O)-, $(C_1$–$C_6)$alkyl-O-NH-(C=O)-, and $(C_1$-$C_6)$alkyl optionally substituted with one to four fluoro moieties;

R^{254} is an $(C_1$-$C_6)$alkyl radical optionally substituted by one to four fluoro substituents; and

R^{255} is a radical selected from the group consisting of H, halo, -OH, $(C_1$-$C_6)$alkyl-O-, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_3$-$C_7)$cycloalkyl, -CN, H-(C=O)-, $(C_1$-$C_6)$alkyl-(C=O)-, $(C_1$-$C_6)$alkyl-(C=O)-O-, HO-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, $(C_1$-$C_6)$alkyl-NH-. [$(C_1$-$C_6)$alkyl]$_2$-N-, $(C_3$-$C_7)$cycloalkyl-NH-, $(C_6$-$C_{10})$aryl-NH-, [$(C_1$-$C_6)$alkyl]-[($(C_6$-$C_{10})$aryl)-N]-, $(C_1$-$C_9)$heteroaryl-NH-, H_2N-(C=O)-, $(C_1$-$C_6)$alkyl-NH-(C=O)-. [$(C_1$-$C_6)$alkyl]$_2$-N-(C=O)-, $(C_6$-$C_{10})$aryl-(C=O)-, [$(C_1$-$C_6)$alkyl]-[($(C_6$-$C_{10})$aryl)-N]-(C=O)-, $(C_1$-$C_6)$alkyl-O-NH-(C=O)-, $(C_1$-$C_6)$alkyl-S-, and $(C_1$-$C_6)$alkyl optionally substituted by one to four fluoro substituents.

[000136] 2-phenylpyran-4-one derivatives such as those described in U.S. Patent No. 6,518,303 are also useful as Cox-2 selective inhibitors of the present invention. Such 2-phenylpyran-4-one derivatives have the general formula shown below in formula **XXXXXIII**:



XXXXXIII

wherein:

R^{256} represents an alkyl or $-NR^{259}R^{260}$ group, wherein R^{259} and R^{260} each independently represents a hydrogen atom or an alkyl group;

R^{257} represents an alkyl, C_3 –C_7 cycloalkyl, naphthyl, tetrahydronaphthyl or indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

R^{258} represents a methyl, hydroxymethyl, alkoxymethyl, C_3 –C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a CH_2 -- R^{261} group wherein R^{261} represents an alkyl group; and

X^{36} represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

[000137] Examples of 2-phenylpyran-4-one derivatives useful in the present invention include, but are not limited to:

3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-bromophenyl)-2-(4-methylsulfonylphenyl)-6-methylpyran-4-one,

3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one ,

2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxypyran-4-one,
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy)pyran-4-one,
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one,
3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-one,
and pharmaceutically acceptable salts thereof.

[000138] Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent No. 6,472,416 (sulfonylphenylpyrazoles); U.S. Patent No. 6,451,794 (2,3-diaryl-pyrazolo[1,5-b]pyridazines); U.S. Patent Nos. 6,169,188, 6,020,343, and 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); and U.S. Patent Nos. 6,359,182 and 6,538,116 (C-nitroso compounds).

[000139] Examples of specific compounds that are useful as Cox-2 selective inhibitors include, without limitation:

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h9) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

[000140] Cox-2 inhibitors that are useful in the methods and compositions of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable. Likewise, Cox-2 inhibitors that are useful in the compositions and methods of present invention can by synthesized, for example, according to the description in **Example 1**. Several Cox-2 inhibitors that are suitable for use with the compositions and methods of the present invention may be synthesized by the methods described in, for example, U.S. Patent No. 5,466,823 to Talley, *et al.* Cox-2 inhibitors can also be isolated and purified from natural sources. Cox-2 inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[000141] Preferred Cox-2 selective inhibitor compounds are those compounds selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, RS 57067, T-614, BMS-347070 (Bristol Meyers Squibb, described in U.S. Patent No. 6,180,651), JTE-522 (Japan Tabacco), S-2474 (Shionogi), SVT-2016, CT-3 (Atlantic Pharmaceutical), ABT-963 (Abbott), SC-58125 (GD Searle), nimesulide, flosulide, NS-398 (Taisho Pharmaceutical), L-745337 (Merck), RWJ-63556, L-784512 (Merck), darbufelone (Pfizer), CS-502 (Sankyo), LAS-34475 (Almirall Prodesfarma), LAS-34555 (Almirall Prodesfarma), S-33516 (Servier), SD-8381 (Pharmacia, described in U.S. Patent No. 6,0340256), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1376 (Chiroscience), L-748731 (Merck), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), prodrugs of any of them, and mixtures thereof.

[000142] More preferred is that the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

[000143] Even more preferred still is that the Cox-2 selective inhibitor is celecoxib.

[000144] Various classes of Cox-2 inhibitors useful in the present invention can be prepared as follows. Pyrazoles can be prepared by methods described in WO 95/15316. Pyrazoles can further be prepared by methods described in WO 95/15315. Pyrazoles can also be prepared by methods described in WO 96/03385.

[000145] Thiophene analogs useful in the present invention can be prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932.

[000146] Oxazoles useful in the present invention can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980.

[000147] Isoxazoles useful in the present invention can be prepared by the methods described in WO 96/25405.

[000148] Imidazoles useful in the present invention can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387.

[000149] Cyclopentene Cox-2 inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentene Cox-2 inhibitors is also described in WO 95/00501.

[000150] Terphenyl compounds useful in the present invention can be prepared by the methods described in WO 96/16934.

[000151] Thiazole compounds useful in the present invention can be prepared by the methods described in WO 96/03,392.

[000152] Pyridine compounds useful in the present invention can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585.

[000153] Benzopyranopyrazolyl compounds useful in the present invention can be prepared by the methods described in WO 96/09304.

[000154] Chromene compounds useful in the present invention can be prepared by the methods described in WO 98/47890. Preparation of chromene compounds is also described in WO 00/23433. Chromene compounds can further be prepared by the methods described in U.S. Patent No. 6,077,850. Preparation of chromene compounds is further described in U.S. Patent No. 6,034,256.

[000155] Arylpyridazinones useful in the present invention can be prepared by the methods described in WO 00/24719. Preparation of arylpyridazinones is also described in WO 99/10332. Arylpyridazinones can further be prepared by the methods described in WO 99/10331.

[000156] 5-Alkyl-2-arylaminophenylacetic acids and derivatives useful in the present invention can be prepared by the methods described in WO 99/11605.

[000157] Diarylmethylidenefuran derivative Cox-2 selective inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 6,180,651.

[000158] The celecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

[000159] The valdecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

[000160] The parecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

[000161] The rofecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,474,995.

[000162] The deracoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

[000163] The etoricoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 98/03484.

[000164] The meloxicam used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,233,299.

[000165] The compound 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,994,381.

[000166] The compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 00/24719.

[000167] The compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one used in the compositions and methods of the present invention can be prepared in the manner set forth in EP 863134.

[000168] The compound 2-[(2-chloro-6-fluorophenyl)amino]-5-methyl-benzeneacetic acid used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 99/11605.

[000169] The compound N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,885,367.

[000170] The compound (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 6,180,651.

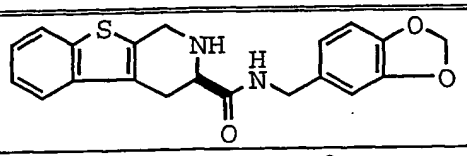
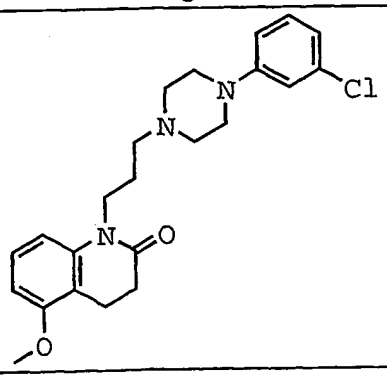
[000171] Another element of the present invention is a 5-HT_{1A} receptor modulator. The expression "5-HT_{1A} receptor" refers to the 5-

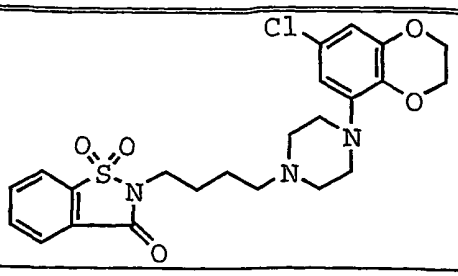
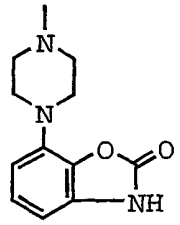
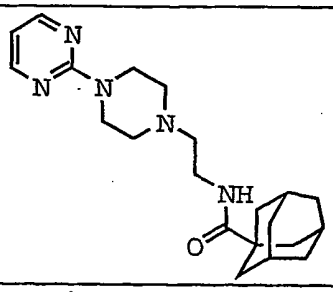
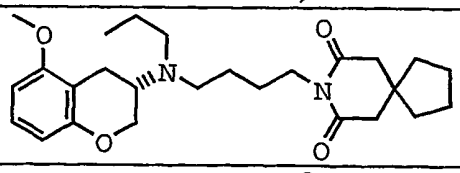
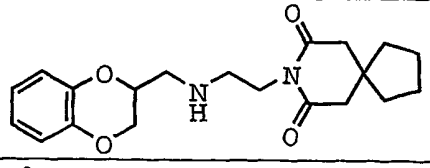
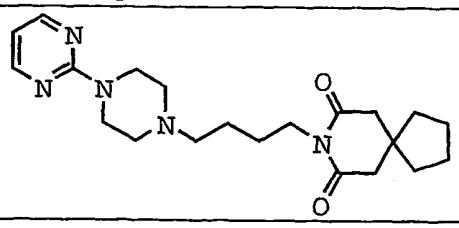
hydroxytryptamine$_{1A}$ receptor, which is pharmacologically characterized by its high affinity for 5-hydroxytryptamine (5-HT, serotonin). The expression "5-HT$_{1A}$ receptor" refers to proteins having amino acid sequences which are substantially similar to native mammalian 5-hydroxytryptamine$_{1A}$ receptors or 5-hydroxytryptamine$_{1A}$ amino acid sequences, and which are capable of binding 5-hydroxytryptamine molecules and inhibiting 5-hydroxytyryptamine from binding to the 5-hydroxytryptamine$_{1A}$ receptor. The human 5-HT$_{1A}$ receptor is located on chromosome 5q11.2-q13 and has 422 amino acids.

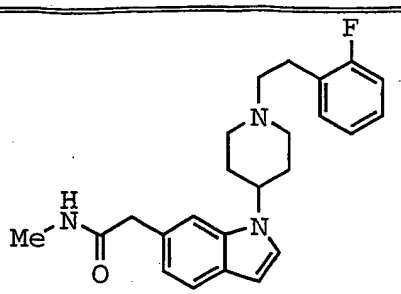
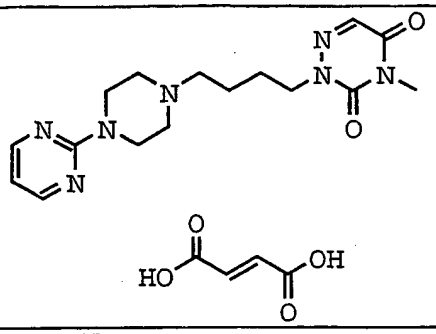
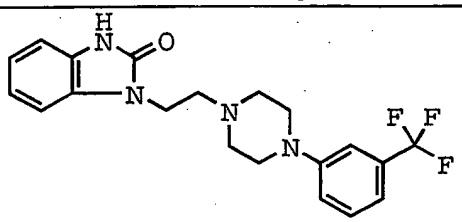
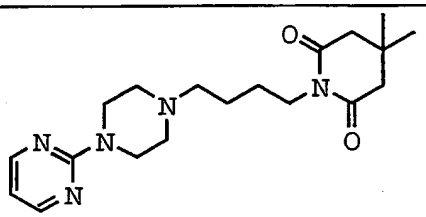
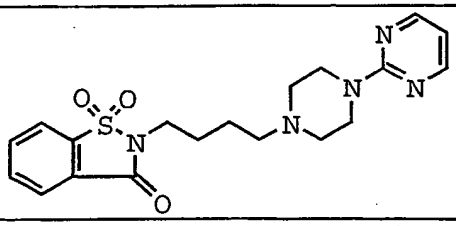
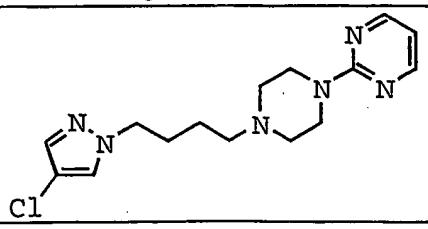
[000172] The expression "5-HT$_{1A}$ receptor modulator" refers to a compound that binds to the 5-HT$_{1A}$ receptor and modulates its activity, with, for example, agonist, reverse agonist, antagonist or mixed effects.

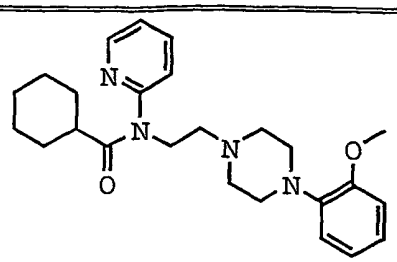
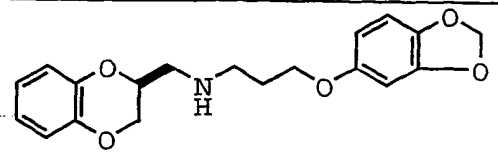
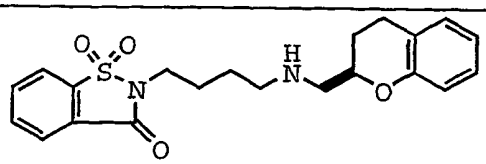
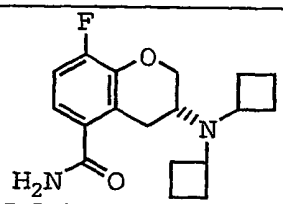
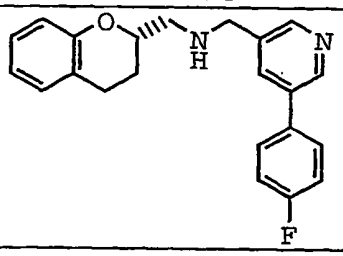
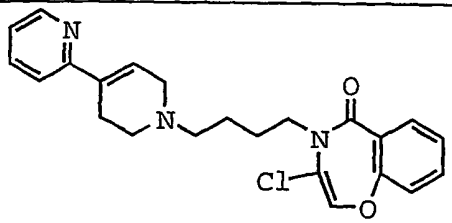
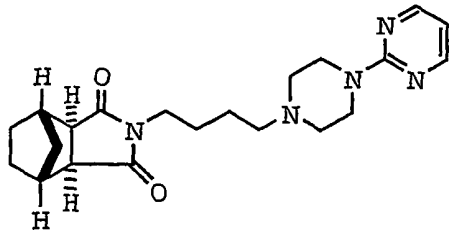
[000173] The structures of some examples of preferred 5-HT$_{1A}$ receptor modulators are listed in Table No. 3 below.

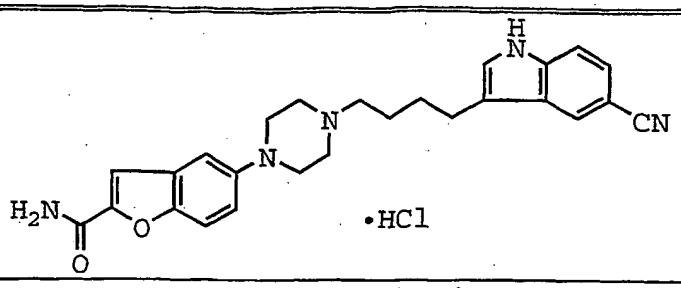
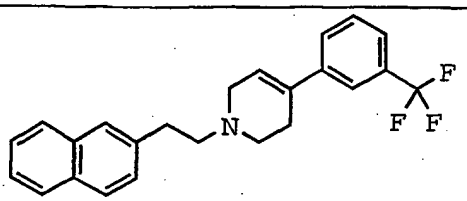
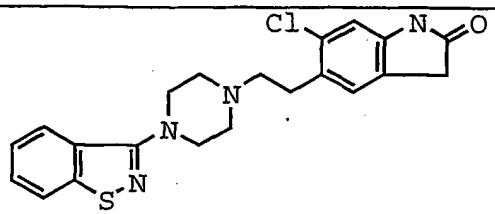
Table 3. Examples of 5-HT$_{1A}$ Receptor Modulators

Compound Number	Structure
H1	
H2	

Compound Number	Structure
H3	
H4	 •HCl
H5	
H6	
H7	
H8	

Compound Number	Structure
H10	
H11	
H12	
H13	
H14	
H15	

Compound Number	Structure
H16	 •3HCl
H17	 •HCl
H18	
H19	
H20	
H22	
H23	

Compound Number	Structure
H24	
H26	
H27	

[000174] The names, CAS registry numbers and references for examples of preferred 5-HT_{1A} receptor modulators are listed in Table.4, below.

Table 4. Examples of preferred 5-HT_{1A} Receptor Modulator Names, CAS Registry Numbers and References

Compound Number	Name(s)	CAS Registry Number	Reference
H1	(R)-N-(1,3-benzodioxol-5-ylmethyl)-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine-3-carboxamide, (AP-521)	151227-58-6	JP07109281
H2	1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1H)-quinolinone (OPC-14523)	145969-30-8	EP512525
H3	2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2H)-one, 1,1-dioxide (DU-125530)	161611-99-0	
H4	7-(4-methyl-1-piperazinyl)-2(3H)benzoxazolone, monohydrochloride (SLV-308)	269718-83-4	WO0029397
H5	adatanserin	127266-56-2	US5010078
H6	alnespirone	138298-79-0	EP452204
H7	binospirone	102908-59-8	EP170213
H8	buspirone	36505-84-7	US3717634
H9	DU-127090	362524-71-8	
H10	2-[1-[1-[2-(2-fluorophenyl)ethyl]piperidino-4-yl]-1H-indol-6-yl]-N-methylacetamide (E-2101)		WO9843956
H11	eptapirone	179756-85-5	WO09616949
H12	flibanserin	167933-07-5	EP526434
H13	gepirone	83928-76-1	US4423049
H14	ipsapirone	95847-70-4	DE3321969
H15	lesopitron	132449-46-8	EP382637
H16	N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamide, trihydrochloride (WAY-100635)	146714-97-8	EP512755
H17	N-[3-(1,3-benzodioxol-5-	137275-80-0	EP452204

Compound Number	Name(s)	CAS Registry Number	Reference
	yloxy)propyl]-2,3-dihydro-(2S)-1,4-benzodioxin-2-methanamine, hydrochloride (MKC-242)		
H18	repinotan (BAY X3702)	144980-29-0	EP749970
H19	robalzotan	169758-66-1	WO0951189 1
H20	sarizotan	177975-08-5	EP707007
H21	SLV-319		
H22	SUN-N4057	182415-09-4	WO9624594
H23	tandospirone	87760-53-0	EP82402
H24	vilazodone	163521-08-2	EP648767
H25	VML-670		
H26	xaliproden	135354-02-8	EP101381
H27	ziprasidone	146939-27-7	US4883795
H28	6-hydroxy-buspirone		US6150365
H29	pyrazolidine derivative		EP736526
H30	Heteroaryloxyethylamines		US6063784
H31	5-hydoxytryptamine, 5-methoxytryptamine, buspirone, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), ipsaspirone, gepirone, SM23997, lysergic acid, diethylamide, and agonistic antibodies		WO9210200
H32	piperazine derivatives		WO9311122
H33	8-(2-aminoalkoxy) fluorochroman derivative		WO9429293
H34	abeo-ergoline derivatives		WO9528403
H35	A-74283	131818-91-2	
H36	AP-159	129592-83-2	
H37	AZ 16596	257864-15-6	
H38	2- [[4-(2-Methoxyphenyl)piperazin-1-yl] methyl] octahydroimidazo [1,5-a] pyridine-1,3-dione (B 20991)		
H39	BMS 181100 (BMY 14802)	105565-56-8	
H40	BMS 181101 (BMY 42569)	146479-45-0	DE03507983
H41	BMS 181970		
H42	1-methyl-4- [7-(4-chlorophenyl)methylaminocarbonyl]		

Compound Number	Name(s)	CAS Registry Number	Reference
	napththyl-piperazine (CP291952)		
H43	(omega-piperazinylalkoxy)alkylenedioxybenzene (BP 554)		JP57080379
H44	E 5165		
H45	E 6265		
H46	Ebalzotan	149494-37-1	
H47	Eltoprazine	98224-03-4	
H48	F 11440	179756-58-2	
H49	F 13714		
H50	Flesinoxan		EP00138280
H51	2- [4-(3-Phenylpyrrolidin-1-yl)butyl] -1,2-benzisothiazol-3(2H)-one 1,1-dioxide (LB 50016)		
H52	LY 41	140221-50-7	
H53	(+/-)-4-Substituted-amino-6-substituted-1,3,4,5-tetrahydrobenz[c,d]inoles (LY 228729)	115994-79-0	EP00153083
H54	LY 228730		
H55	LY 274600	132873-35-9	
H56	LY 274601	132873-34-8	
H57	LY 293284	141318-62-9	
H58	6-Heterocyclyl-4-amino-1,3,4,5-tetrahydrobenz CD indoles (LY 297996)	156896-33-2	EP00590971
H59	Isoxazole derivatives (LY 315535)		US5434174
H60	hetero-oxy alkanamines (LY 333068)		EP00722941
H61	LY 426965	326821-27-6	
H62	LY 433221		
H63	MDL 72832	113777-33-6	
H64	MDL 73975	159650-30-3	
H65	NDL 249	169758-71-8 184675-01-2	
H66	Nerisopam	102771-12-0	
H67	Org 1301	142494-12-0	
H68	2-(2-oxo-hexahydropyrimidin-1-yl)propylaminomethyl-benzopyran (R 137696)		

Compound Number	Name(s)	CAS Registry Number	Reference
H69	RU 24969	66611-26-5 107008-28-6	
H70	1-[[5-[[4-substituted-1-piperazinyl]methyl]-pyrrol-2-yl or furan-2-yl]methyl-2-piperidinones (RWJ 25730)		US4992441
H71	S 14489	153607-44-4	
H72	1-Naphthyl-piperazine derivatives (S 14506)	135721-98-1	EP00434561
H73	1-Naphthyl-piperazine derivatives (S 14671)	135722-27-9	EP00434561
H74	S 15535	146998-34-7	
H75	S 15931	153607-45-5	
H76	8- [4- [N-(5-Acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)-Npropylamino] butyl] -8-azaspiro [4.5] decane-7,9-dione (S 23751)		
H77	SDZ 216-525	141533-35-9	
H78	SEP 109235		
H79	SR 59026		
H80	Sunepitron	131744-27-9	
H81	UH 301	127126-21-0 135308-68-8 187593-75-5	
H82	WAY 100135	133025-23-7	
H83	WAY 100802		
H84	Zalospirone		GB02181731

[000175] Also useful as a 5-HT_{1A} receptor modulator in the present invention is [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)amino]-methyl)piperidin-1-yl]-methadone] (F 13640), as described in Colpaert, F. C. *et al, Neuropharmacology, 43*:945-958 (2002).

[000176] Especially preferred 5-HT_{1A} receptor modulators for the present invention include buspirone, gepirone, repinotan, tandospirone, xaliproden and ziprasidone.

[000177] The compounds useful in the present invention optiontionally can have no asymmetric carbon atoms, or, alternatively, the useful compounds can have one or more asymmetric carbon atoms. When the

useful compounds have one or more asymmetric carbon atoms, they therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

[000178] Isomers may include geometric isomers, for example cis-isomers or trans-isomers across a double bond. All such isomers are contemplated among the compounds useful in the present invention.

[000179] Also included in the methods, combinations and compositions of the present invention are the isomeric forms and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric and galacturonic acids.

[000180] Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art

by conventional means from the corresponding compound of the present invention.

[000181] Also included in the methods, combinations and compositions of the present invention are the prodrugs of the described compounds and the pharmaceutically-acceptable salts thereof. The term "prodrug" refers to drug precursor compounds which, following administration to a subject and subsequent absorption, are converted to an active species *in vivo* via some process, such as a metabolic process. Other products from the conversion process are easily disposed of by the body. More preferred prodrugs produce products from the conversion process that are generally accepted as safe. A nonlimiting example of a "prodrug" that will be useful in the methods, combinations and compositions of the present invention is parecoxib (N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propanamide), which is a prodrug for valdecoxib.

[000182] The methods and combinations of the present invention are useful for the treatment or prevention of pain, inflammation, or inflammation-related disorder. In a preferred embodiment, the subject is one that is in need of treatment or prevention of pain, inflammation, or an inflammation-related disorder.

[000183] The methods and combinations of the present invention are also useful for the treatment or prevention of neurologic disease involving neurodegeneration.

[000184] The phrase "combination therapy" (or "co-therapy") embraces the administration of a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours,

days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single dosage form, such as a capsule, for example, having a fixed ratio of each therapeutic agent or in multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies.

[000185] The phrase "therapeutically effective" is intended to qualify the amount of compounds utilized in the therapy. This amount will achieve the goal of treating or preventing pain, inflammation or an inflammation-related disorder.

[000186] "Therapeutic compound" means a compound useful in the treatment or prevention of pain, inflammation or an inflammation-related disorder, or of a neurologic disorder involving neurodegeneration.

[000187] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[000188] The term "comprising" means "including the following elements but not excluding others."

Combinations and Methods:

[000189] Among its several embodiments, the present invention provides a composition comprising Cox-2 inhibitor and a 5-HT_{1A} receptor modulator. It is preferred that the composition provides an amount of the Cox-2 inhibitor and an amount of the 5-HT_{1A} receptor modulator wherein the amount of the Cox-2 inhibitor and the amount of the 5-HT_{1A} receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation, or an inflammation-related

disorder, and for the treatment or prevention of a neurologic disorder involving neurodegeneration.

[000190] In one embodiment, the Cox-2 inhibitor compound is a non-steroidal anti-inflammatory drug.

[000191] In another embodiment, the Cox-2 inhibitor is a Cox-2 selective inhibitor.

[000192] In still another embodiment, the the Cox-2 inhibitor compound is a prodrug of a Cox-2 inhibitor compound, illustrated herein with parecoxib.

[000193] In yet another embodiment, the present invention further provides a combination therapy method for the treatment or prevention of pain, inflammation, or an inflammation-related disorder in a mammal in need thereof, comprising administering to the mammal an amount of a Cox-2 inhibitor and an amount of a 5-HT_{1A} receptor modulator wherein the amount of the Cox-2 inhibitor and the amount of the 5-HT_{1A} receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation, or an inflammation-related disorder.

[000194] In a further embodiment, the present invention provides a pharmaceutical composition for the treatment or prevention of pain, inflammation, or an inflammation-related disorder comprising an amount of a Cox-2 inhibitor and an amount of a 5-HT_{1A} receptor modulator and a pharmaceutically-acceptable excipient.

[000195] In still further embodiment, the present invention provides a kit that is suitable for use in the treatment, prevention or inhibition of pain, inflammation, or an inflammation-related disorder wherein the kit comprises a first dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a 5-HT_{1A} receptor modulator, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention or inhibition of pain, inflammation, or an inflammation-related disorder.

[000196] The methods and compositions of the present invention provide one or more benefits. Combinations of Cox-2 inhibitors and 5-HT_{1A} receptor modulators are useful in treating and preventing pain, inflammation, or an inflammation-related disorder. Preferably, the Cox-2 inhibitors and the 5-HT_{1A} receptor modulators of the present invention are administered in combination at a low dose, that is, at a dose lower than has been conventionally used in clinical situations.

[000197] The combinations of the present invention will have a number of uses. For example, through dosage adjustment and medical monitoring, the individual dosages of the therapeutic compounds used in the combinations of the present invention will be lower than are typical for dosages of the therapeutic compounds when used in monotherapy. The dosage lowering will provide advantages including reduction of side effects of the individual therapeutic compounds when compared to the monotherapy. In addition, fewer side effects of the combination therapy compared with the monotherapies will lead to greater subject compliance with therapy regimens.

[000198] Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at higher doses.

[000199] When administered as a combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

[000200] Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid that are used in the treatment, prevention or reduction of pain, inflammation, or an inflammation-related disorder may inhibit enzyme activity through a variety of mechanisms. By way of example, the cyclooxygenase-2 inhibitors used in the methods described herein may block the enzyme activity directly by binding at the substrate site of the enzyme. The use of a Cox-2 selective inhibiting agent is highly advantageous in that it minimizes the gastric side effects that can occur

with non-selective non-steroidal antiinflammatory drugs (NSAIDs), especially where prolonged treatment is expected.

[000201] Besides being useful for human treatment, these methods are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, avians, and the like. More preferred animals include horses, dogs, and cats.

[000202] As used herein, the terms "therapeutically effective amount" are intended to qualify the amount of a Cox-2 inhibiting agent and a 5-HT_{1A} receptor modulator that are required to treat or prevent pain, inflammation, or an inflammation-related disorder, or to treat or prevent neurologic disease involving neurodegeneration.

[000203] The combinations and methods of the present invention would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-related disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

[000204] Such combinations and methods of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, overactive bladder (OAB), preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, UV damage, burns and dermatitis, and postoperative inflammation including ophthalmic surgery such as cataract surgery and refractive surgery.

[000205] Combinations and methods of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

[000206] Combinations and methods of the invention would be useful in treating inflammation in such diseases as migraine headaches, polyarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

[000207] The combinations and methods of the invention would also be useful in the treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, glaucoma and acute injury to the eye tissue.

[000208] The combinations and methods would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as associated with osteoporosis.

[000209] The combinations and methods of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These combinations and methods would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and liver disease.

[000210] The combinations and methods would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, dysmennorrhea, neuropathic pain and pain resulting from cancer.

[000211] The combinations and methods above would be useful for, but not limited to, treating and preventing inflammation-related cardiovascular disorders in a subject. The combinations and methods would be useful for treatment and prevention of vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke

(hemorrhagic or ischemic), thrombosis, including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

[000212] The combinations and methods would be useful for, but not limited to, the treatment and prevention of angiogenesis-related disorders in a subject. According to the present invention, the compounds can be administered to a subject in need of angiogenesis inhibition. The method would be useful for treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

[000213] Compounds of the invention would be useful for the prevention or treatment of benign and malignant tumors/neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophogeal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Preferably, neoplasia is selected from gastrointestinal cancer,

Barrett's esophagus, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers. The compounds can also be used to treat the fibrosis which occurs with radiation therapy. The method can be used to treat subjects having adenomatous polyps, including those with sporadic adenomatous polyposis (SAP) or familial adenomatous polyposis (FAP). Additionally, the method can be used to prevent polyps from forming in subjects at risk of FAP.

[000214] The combinations and methods of the present invention are useful for the prevention and treatment of pain, inflammation and central nervous system (CNS) disorders, which include, for example, adjustment disorders, such as anxiety (mixed anxiety), mood (depressed), conduct disturbance, mixed anxiety and mood (conduct); addictive disorders, such as alcohol abuse, intoxication disorders, nicotine abuse, psychoactive substances abuse and substance disorder; withdrawal syndromes; acute trauma; age associated mental disorders, such as learning and Alzheimer's disease; agitation disorders, such as agitation in Alzheimer's disease and agitation in the elderly; aggressive behavior, such as in Alzheimers disease; amyloidosis, such as aging / senile, hereditary, immunocyte derived, lichen, primary, reactive systemic, secondary, senile (Alzheimer's disease), amyotrophy & amyotropic lateral sclerosis (ALS), and anorexia nervosa; anxiety disorders, such as generalized anxiety disorder (GAD), panic disorder, bipolar disorder, social phobias and stress related diseases; apathy; attention deficit disorder (ADD); attention deficit hyperactivity disorder (ADHD); autism; auto immune disorders, such as lupus erythematosis and multiple sclerosis; behavioral disturbances, such as agitation plus diminished cognition, bipolar I disorder and bipolar II disorder; bulimia nervosa; cardiovascular; blood pressure modification, such as for hypertension, hypotension and heart rate modification; chemotherapy-induced vomiting; chronic fatigue immune disorders (CFIDS); chronic fatigue syndrome (CFS); cognitive dysfunction, such as

cortical dementias including mild cognitive impairment (MCI), Lewy Body dementia, vascular dementia, neurodegeneration, and cognitive dysfunction resulting from stroke, ischemia, trauma, or surgical procedures, including coronary artery bypass surgery; cognition enhancement; conduct disorder; cyclothymia; delusional disorder; depression, such as adolescent, in Alzheimer's disease, general, minor, in Parkinson's disease and diabetic neuropathy; dissociative disorders; developmental disorders, such as learning disabilities, language disorders and mental retardation; dementia, such as associated with aging, illness, neurodegeneration and dyskensia; dysthymia; dystonia; eating disorders, such as anorexia nervosa, bulimia nervosa, obesity, epilepsy and fibromyalgia syndrome (FMS); gastrointestinal disorders, such as irritable bowel syndrome, psychogenic effects and stress-related; growth retardation effects, such as endocrine, psychosocial and stress-related; heart rate modification; Huntington's Chorea; hypertension; immune system disorders, such as immune system depression; impulse control (related to conduct disorder); incontinence, such as mixed states, stress incontinence and urge incontinence; infectious neuropathy, such as AIDS; carpal tunnel syndrome; dementia; irritable bowel syndrome (IBS), such as constipative and diarrhea-predominant; inflammatory bowel disease (IBD), such as constipation-predominant, diarrhea-predominant and mixed states; inhalation disorder; lactation inhibition, metabolic & chromosomal disorders, such as galactosemia phenylketonuria, fatty acid disorder, infantile nephropathic cystinosis, orthithrotranscarbamylase porphyria and migrane; mood disorders, such as atypical depression, bipolar disorder (including pychotic features), major depressive disorder, mania, and seasonal affective disorder; movement disorders, such as athetosis, chorea, dyskinesia, dystonia, restless leg syndrome (RLS), tremor plus periodic limb movement (PLM), periodic limb movements of sleep (PLMS), Huntington's chorea, Parkinson's disease, PLM, PLMS, progressive supranuclear palsy, stereotypy (various), torticollis, tic disorders and tremor; multisystemic atrophy (MSA), such as multiple sclerosis;

neuroendocrine system disorders; neurologic diseases involving neurodegeneration, such as amyotrophy, amyotrophy diabetics, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Huntington's chorea and Parkinson's disease; neurological disorders; neuropathy, such as diabetic and peripheral; neuroprotective effects, such as for ischemic brain injury, myocardial infarction, spinal cord injury, traumatic brain injury and obesity; obsessive compulsive disorder (OCD); oncology related disorders, such as with behavior abnormalities resulting from tumors or treatments, such as chemotherapy and induced vomiting; oppositional defiant disorder; pain disorders, such as acute, chronic, cluster headache, dysmenorrhea, labor, migraine, neuropathic, AIDs-related, cancer-related, chemotherapeutic-induced, diabetic, post-herpetic neuralgia, radiation-induced, osteoarthritis flare, phantom limb, surgical, post-surgical and incisional, psychic, regional pain (such as abdominal region, chronic back pain, complex-regional pain disorder, dental, face and mouth, head, lower back and peripheral), rheumatoid arthritis, starting pain and systematic pain (such as in connective tissue, such as musculoskeletal, nervous system, urogenital, uterine contractions); panic disorder, such as with agoraphobia and without agoraphobia; Parkinson's disease; peripheral neuropathy; personality disorders; phobias (simple), such as phobias of animals, closed spaces (claustrophobia), heights (acrophobia), public places (agoraphobia); phobias (Social), such as, public eating, public embarrassment, public performance / speaking and using public lavatories; SSRI poop out syndrome; post-traumatic stress disorder; progressive supranuclear palsy (PSP); prolactin plasma level disorders; psychotic disorders, such as brief and long duration, due to medical condition, not otherwise specified (NOS) and restless leg syndrome (RLS); schizophrenias, such as delusional (paranoid) disorder, schizoaffective disorders, schizophreniform disorders and seasonal affective disorder; seizure disorders, such as epilepsy (partial) and epilepsy (generalized); sexual dysfunction, such as for female and for male; sleep disorders, such as apnea, parasomnias, insomnia, narcolepsy, obstructive, and disorders

of circadian rhythm, enuresis, initiation and maintenance; social phobias, such as social anxiety disorder; somatoform disorders, such as conversion, body, dysmorphic, fibromyalgia syndrome (FMS), hypochondriasis, NOS, somatization and undifferentiated; specific developmental disorders; stress disorders, such as acute, chronic and incontinence; spectrum disorders; stroke; suicidal behavior, and in particular, prevention of and amelioration of; thyroid stimulating hormone disorders (TSH); Tourette's syndrome; tooth-germ morphogenesis disorders; thermoregulation disorders; TSH modulating agent disorders; tic disorders; trauma, such as acute head, and related effects, such as blood pressure regulation, cerebral blood flow, CSF production, inflammation, and ischemia; vasospasms; vasoreactive headaches and violent behavior.

[000215] As used herein, the term "treatment" includes partial or total inhibition of the dementia or cognitive dysfunction, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, and senile dementia.

[000216] The combinations and methods of the present invention are particularly useful for the treatment, prevention or inhibition of a central nervous system disorder associated with stroke (ischemic or hemmorhagic) or other ischemic brain injury.

[000217] The phrases "low dose" or "low dose amount", in characterizing a therapeutically effective amount of the Cox-2 selective inhibitor and the 5-HT_{1A} receptor modulator or therapy in the combination therapy, defines a quantity of such agent, or a range of quantity of such agent, that is capable of reducing the discomfort of pain, inflammation, or an inflammation-related disorder while optionally reducing or avoiding one or more side effects of monotherapy with a 5-HT_{1A} receptor modulator or other pain-relieving agent. Side effects of 5-HT_{1A} receptor modulators that the selected combinations of the present invention may reduce or avoid are nausea, dizziness, insomnia, headache, fatigue, paresthesias, uneasiness, nervousness, lightheadedness, excitement, tachycardia,

malaise, dysphoria, dry mouth, headache, somnolence, constipation, abnormal movements, respiratory disorders, dyspepsia, skin rash, elevations in liver enzymes and gastrointestinal disturbances.

[000218] The phrase "adjunctive therapy" encompasses treatment of a subject with agents that reduce or avoid side effects associated with the combination therapy of the present invention.

Dosages, Formulations and Routes of Administration:

[000219] Dosage levels of the Cox-2 inhibiting agent (*e.g.*, a Cox-2 selective inhibiting agent or a prodrug of a Cox-2 selective inhibiting agent) on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 1.0 mg to about 1,000 mg. While the dosage of active compound administered to a warm-blooded animal (a mammal), is dependent on the species of that mammal, the body weight, age, and individual condition, and on the route of administration, the unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 500 mg of the active ingredient (for example, Cox-189). The amount of active ingredient that may be combined with a 5-HT_{1A} receptor modulator to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[000220] A total daily dose of a 5-HT_{1A} receptor modulator can generally be in the range of from about 0.001 to about 10,000 mg/day in single or divided doses, with preferred levels of about 1.0 mg to about 1,000 mg. It is understood, however, that specific dose levels of the therapeutic agents or therapeutic approaches of the present invention for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the drug combination, and the severity of the particular disease being treated and form of administration.

[000221] Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from *in vitro* initially can provide useful guidance on the proper doses for subject administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of pain, inflammation, or an inflammation-related disorder in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular subject, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective *in vitro*. Thus, where a compound is found to demonstrate *in vitro* activity at, *e.g.*, 10 μM, one will desire to administer an amount of the drug that is effective to provide about a 10 μM concentration *in vivo*. Determination of these parameters is well within the skill of the art.

[000222] Effective formulations and administration procedures are well known in the art and are described in standard textbooks.

[000223] The Cox-2 inhibiting agents or the 5-HT_{1A} receptor modulators can be formulated as a single pharmaceutical composition or as independent multiple pharmaceutical compositions. Pharmaceutical compositions according to the present invention include those suitable for oral, inhalation spray, rectal, topical, buccal (*e.g.*, sublingual), or parenteral (*e.g.*, subcutaneous, intramuscular, intravenous, intrathecal, intramedullary and intradermal injections, or infusion techniques) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral or parenteral.

[000224] Compounds and composition of the present invention can then be administered orally, by inhalation spray, rectally, topically, buccally or

parenterally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The compounds of the present invention can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic compounds or as a combination of therapeutic compounds.

[000225] Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation.

[000226] The compounds useful in the methods, combinations and compositions of the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well-known techniques of pharmacy, consisting essentially of admixing the components.

[000227] The amount of compound in combination that is required to achieve the desired biological effect will, of course, depend on a number of factors such as the specific compound chosen, the use for which it is intended, the mode of administration, and the clinical condition of the recipient.

[000228] The compounds of the present invention can be delivered orally either in a solid, in a semi-solid, or in a liquid form. Dosing for oral administration may be with a regimen calling for single daily dose, or for a single dose every other day, or for multiple, spaced doses throughout the

day. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. Capsules, tablets, etc., can be prepared by conventional methods well known in the art. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient or ingredients. Examples of dosage units are tablets or capsules, and may contain one or more therapeutic compounds in an amount described herein. For example, in the case of a 5-HT_{1A} receptor modulator, the dose range may be from about 0.01 mg to about 5,000 mg or any other dose, dependent upon the specific inhibitor, as is known in the art. When in a liquid or in a semi-solid form, the combinations of the present invention can, for example, be in the form of a liquid, syrup, or contained in a gel capsule (*e.g.*, a gel cap). In one embodiment, when a 5-HT_{1A} receptor modulator is used in a combination of the present invention, the 5-HT_{1A} receptor modulator can be provided in the form of a liquid, syrup, or contained in a gel capsule. In another embodiment, when a Cox-2 inhibiting agent is used in a combination of the present invention, the Cox-2 inhibiting agent can be provided in the form of a liquid, syrup, or contained in a gel capsule.

[000229] Oral delivery of the combinations of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. For some of the therapeutic compounds useful in the methods, combinations and compositions of the present invention the intended effect is to extend the time period over which the active drug molecule is delivered to the site of action by manipulation of

the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

[000230] Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one therapeutic compound useful in the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more assessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

[000231] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[000232] Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[000233] Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection or by infusion. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 10% w/w of a compound disclosed herein.

[000234] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[000235] The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. A suitable daily dose of each active therapeutic compound is one that achieves the same blood serum level as produced by oral administration as described above.

[000236] The dose of any of these therapeutic compounds can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 10,000 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampules for injection can contain, for example, from about 1 mg to about 100 mg.

[000237] Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound or compounds of the present invention with one or more conventional solid carriers, for example, cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug; and then shaping the resulting mixture.

[000238] Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include petroleum jelly (*e.g.*, Vaseline), lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound or compounds are generally present at a concentration of from 0.1 to 50% w/w of the composition, for example, from 0.5 to 2%.

[000239] Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound or compounds of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound or compounds is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound or compounds can be

delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

[000240] In any case, the amount of active ingredients that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

[000241] In combination therapy, administration of two or more of the therapeutic agents useful in the methods, combinations and compositions of the present invention may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or in a separate formulation. Independent administration of each therapeutic agent may be accomplished by, for example, oral, inhalation spray, rectal, topical, buccal (*e.g.*, sublingual), or parenteral (*e.g.*, subcutaneous, intramuscular, intravenous, intrathecal, intramedullary and intradermal injections, or infusion techniques) administration. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. Solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropylmethyl cellulose, together with one or more of a lubricant, preservative, surface active or dispersing agent. The therapeutic compounds may further be administered by any combination of, for example, oral/oral, oral/parenteral, or parenteral/parenteral route.

[000242] The therapeutic compounds which make up the combination therapy may be a combined dosage form or in separate dosage forms intended for substantially simultaneous oral administration. The therapeutic compounds which make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two step ingestion. Thus, a regimen may call for sequential administration of the therapeutic compounds with spaced-apart ingestion of the separate, active agents. The time period

between the multiple ingestion steps may range from, for example, a few minutes to several hours to days, depending upon the properties of each therapeutic compound such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the therapeutic compound, as well as depending upon the effect of food ingestion and the age and condition of the subject. Circadian variation of the target molecule concentration may also determine the optimal dose interval. The therapeutic compounds of the combined therapy whether administered simultaneously, substantially simultaneously, or sequentially, may involve a regimen calling for administration of one therapeutic compound by oral route and another therapeutic compound by intravenous route. Whether the therapeutic compounds of the combined therapy are administered orally, by inhalation spray, rectally, topically, buccally (*e.g.*, sublingual), or parenterally (*e.g.*, subcutaneous, intramuscular, intravenous and intradermal injections, or infusion techniques), separately or together, each such therapeutic compound will be contained in a suitable pharmaceutical formulation of pharmaceutically-acceptable excipients, diluents or other formulations components. Examples of suitable pharmaceutically-acceptable formulations containing the therapeutic compounds are given above. Additionally, drug formulations are discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975. Another discussion of drug formulations can be found in Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

[000243] The following examples describe preferred embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, taken together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples, all percentages are given on a weight basis, unless otherwise indicated.

EXAMPLE 1

[000244] This example illustrates combinations of the present invention.

[000245] Table 5 describes a number of combinations comprising a Cox-2 selective inhibitor and a 5-HT_{1A} receptor modulator. Designations of "H" correspond to compounds described above in the specification.

Table 5. Combinations of Cox-2 selective inhibiting agents and 5-HT_{1A} receptor modulators.

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
1	Celecoxib	H1
2	Celecoxib	H2
3	Celecoxib	H3
4	Celecoxib	H4
5	Celecoxib	H5
6	Celecoxib	H6
7	Celecoxib	H7
8	Celecoxib	H8
9	Celecoxib	H9
10	Celecoxib	H10
11	Celecoxib	H11
12	Celecoxib	H12
13	Celecoxib	H13
14	Celecoxib	H14
15	Celecoxib	H15
16	Celecoxib	H16
17	Celecoxib	H17
18	Celecoxib	H18
19	Celecoxib	H19
20	Celecoxib	H20
21	Celecoxib	H21
22	Celecoxib	H22
23	Celecoxib	H23
24	Celecoxib	H24

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
25	Celecoxib	H25
26	Celecoxib	H26
27	Celecoxib	H27
28	Celecoxib	H28
29	Celecoxib	H29
30	Celecoxib	H30
31	Celecoxib	H31
32	Celecoxib	H32
33	Celecoxib	H33
34	Celecoxib	H34
35	Celecoxib	H35
36	Celecoxib	H36
37	Celecoxib	H37
38	Celecoxib	H38
39	Celecoxib	H39
40	Celecoxib	H40
41	Celecoxib	H41
42	Celecoxib	H42
43	Celecoxib	H43
44	Celecoxib	H44
45	Celecoxib	H45
46	Celecoxib	H46
47	Celecoxib	H47
48	Celecoxib	H48
49	Celecoxib	H49
50	Celecoxib	H50
51	Celecoxib	H51
52	Celecoxib	H52
53	Celecoxib	H53
54	Celecoxib	H54
55	Celecoxib	H55
56	Celecoxib	H56
57	Celecoxib	H57

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
58	Celecoxib	H58
59	Celecoxib	H59
60	Celecoxib	H60
61	Celecoxib	H61
62	Celecoxib	H62
63	Celecoxib	H63
64	Celecoxib	H64
65	Celecoxib	H65
66	Celecoxib	H66
67	Celecoxib	H67
68	Celecoxib	H68
69	Celecoxib	H69
70	Celecoxib	H70
71	Celecoxib	H71
72	Celecoxib	H72
73	Celecoxib	H73
74	Celecoxib	H74
75	Celecoxib	H75
76	Celecoxib	H76
77	Celecoxib	H77
78	Celecoxib	H78
79	Celecoxib	H79
80	Celecoxib	H80
81	Celecoxib	H81
82	Celecoxib	H82
83	Celecoxib	H83
84	Celecoxib	H84
85	Valdecoxib	H1
86	Valdecoxib	H2
87	Valdecoxib	H3
88	Valdecoxib	H4
89	Valdecoxib	H5
90	Valdecoxib	H6

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
91	Valdecoxib	H7
92	Valdecoxib	H8
93	Valdecoxib	H9
94	Valdecoxib	H10
95	Valdecoxib	H11
96	Valdecoxib	H12
97	Valdecoxib	H13
98	Valdecoxib	H14
99	Valdecoxib	H15
100	Valdecoxib	H16
101	Valdecoxib	H17
102	Valdecoxib	H18
103	Valdecoxib	H19
104	Valdecoxib	H20
105	Valdecoxib	H21
106	Valdecoxib	H22
107	Valdecoxib	H23
108	Valdecoxib	H24
109	Valdecoxib	H25
110	Valdecoxib	H26
111	Valdecoxib	H27
112	Valdecoxib	H28
113	Valdecoxib	H29
114	Valdecoxib	H30
115	Valdecoxib	H31
116	Valdecoxib	H32
117	Valdecoxib	H33
118	Valdecoxib	H34
119	Valdecoxib	H35
120	Valdecoxib	H36
121	Valdecoxib	H37
122	Valdecoxib	H38
123	Valdecoxib	H39

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
124	Valdecoxib	H40
125	Valdecoxib	H41
126	Valdecoxib	H42
127	Valdecoxib	H43
128	Valdecoxib	H44
129	Valdecoxib	H45
130	Valdecoxib	H46
131	Valdecoxib	H47
132	Valdecoxib	H48
133	Valdecoxib	H49
134	Valdecoxib	H50
135	Valdecoxib	H51
136	Valdecoxib	H52
137	Valdecoxib	H53
138	Valdecoxib	H54
139	Valdecoxib	H55
140	Valdecoxib	H56
141	Valdecoxib	H57
142	Valdecoxib	H58
143	Valdecoxib	H59
144	Valdecoxib	H60
145	Valdecoxib	H61
146	Valdecoxib	H62
147	Valdecoxib	H63
148	Valdecoxib	H64
149	Valdecoxib	H65
150	Valdecoxib	H66
151	Valdecoxib	H67
152	Valdecoxib	H68
153	Valdecoxib	H69
154	Valdecoxib	H70
155	Valdecoxib	H71
156	Valdecoxib	H72

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
157	Valdecoxib	H73
158	Valdecoxib	H74
159	Valdecoxib	H75
160	Valdecoxib	H76
161	Valdecoxib	H77
162	Valdecoxib	H78
163	Valdecoxib	H79
164	Valdecoxib	H80
165	Valdecoxib	H81
166	Valdecoxib	H82
167	Valdecoxib	H83
168	Valdecoxib	H84
169	Parecoxib	H1
170	Parecoxib	H2
171	Parecoxib	H3
172	Parecoxib	H4
173	Parecoxib	H5
174	Parecoxib	H6
175	Parecoxib	H7
176	Parecoxib	H8
177	Parecoxib	H9
178	Parecoxib	H10
179	Parecoxib	H11
180	Parecoxib	H12
181	Parecoxib	H13
182	Parecoxib	H14
183	Parecoxib	H15
184	Parecoxib	H16
185	Parecoxib	H17
186	Parecoxib	H18
187	Parecoxib	H19
188	Parecoxib	H20
189	Parecoxib	H21

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
190	Parecoxib	H22
191	Parecoxib	H23
192	Parecoxib	H24
193	Parecoxib	H25
194	Parecoxib	H26
195	Parecoxib	H27
196	Parecoxib	H28
197	Parecoxib	H29
198	Parecoxib	H30
199	Parecoxib	H31
200	Parecoxib	H32
201	Parecoxib	H33
202	Parecoxib	H34
203	Parecoxib	H35
204	Parecoxib	H36
205	Parecoxib	H37
206	Parecoxib	H38
207	Parecoxib	H39
208	Parecoxib	H40
209	Parecoxib	H41
210	Parecoxib	H42
211	Parecoxib	H43
212	Parecoxib	H44
213	Parecoxib	H45
214	Parecoxib	H46
215	Parecoxib	H47
216	Parecoxib	H48
217	Parecoxib	H49
218	Parecoxib	H50
219	Parecoxib	H51
220	Parecoxib	H52
221	Parecoxib	H53
222	Parecoxib	H54

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
223	Parecoxib	H55
224	Parecoxib	H56
225	Parecoxib	H57
226	Parecoxib	H58
227	Parecoxib	H59
228	Parecoxib	H60
229	Parecoxib	H61
230	Parecoxib	H62
231	Parecoxib	H63
232	Parecoxib	H64
233	Parecoxib	H65
234	Parecoxib	H66
235	Parecoxib	H67
236	Parecoxib	H68
237	Parecoxib	H69
238	Parecoxib	H70
239	Parecoxib	H71
240	Parecoxib	H72
241	Parecoxib	H73
242	Parecoxib	H74
243	Parecoxib	H75
244	Parecoxib	H76
245	Parecoxib	H77
246	Parecoxib	H78
247	Parecoxib	H79
248	Parecoxib	H80
249	Parecoxib	H81
250	Parecoxib	H82
251	Parecoxib	H83
252	Parecoxib	H84
253	Deracoxib	H1
254	Deracoxib	H2
255	Deracoxib	H3

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
256	Deracoxib	H4
257	Deracoxib	H5
258	Deracoxib	H6
259	Deracoxib	H7
260	Deracoxib	H8
261	Deracoxib	H9
262	Deracoxib	H10
263	Deracoxib	H11
264	Deracoxib	H12
265	Deracoxib	H13
266	Deracoxib	H14
267	Deracoxib	H15
268	Deracoxib	H16
269	Deracoxib	H17
270	Deracoxib	H18
271	Deracoxib	H19
272	Deracoxib	H20
273	Deracoxib	H21
274	Deracoxib	H22
275	Deracoxib	H23
276	Deracoxib	H24
277	Deracoxib	H25
278	Deracoxib	H26
279	Deracoxib	H27
280	Deracoxib	H28
281	Deracoxib	H29
282	Deracoxib	H30
283	Deracoxib	H31
284	Deracoxib	H32
285	Deracoxib	H33
286	Deracoxib	H34
287	Deracoxib	H35
288	Deracoxib	H36

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
289	Deracoxib	H37
290	Deracoxib	H38
291	Deracoxib	H39
292	Deracoxib	H40
293	Deracoxib	H41
294	Deracoxib	H42
295	Deracoxib	H43
296	Deracoxib	H44
297	Deracoxib	H45
298	Deracoxib	H46
299	Deracoxib	H47
300	Deracoxib	H48
301	Deracoxib	H49
302	Deracoxib	H50
303	Deracoxib	H51
304	Deracoxib	H52
305	Deracoxib	H53
306	Deracoxib	H54
307	Deracoxib	H55
308	Deracoxib	H56
309	Deracoxib	H57
310	Deracoxib	H58
311	Deracoxib	H59
312	Deracoxib	H60
313	Deracoxib	H61
314	Deracoxib	H62
315	Deracoxib	H63
316	Deracoxib	H64
317	Deracoxib	H65
318	Deracoxib	H66
319	Deracoxib	H67
320	Deracoxib	H68
321	Deracoxib	H69

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
322	Deracoxib	H70
323	Deracoxib	H71
324	Deracoxib	H72
325	Deracoxib	H73
326	Deracoxib	H74
327	Deracoxib	H75
328	Deracoxib	H76
329	Deracoxib	H77
330	Deracoxib	H78
331	Deracoxib	H79
332	Deracoxib	H80
333	Deracoxib	H81
334	Deracoxib	H82
335	Deracoxib	H83
336	Deracoxib	H84
337	Etorixocib	H1
338	Etorixocib	H2
339	Etorixocib	H3
340	Etorixocib	H4
341	Etorixocib	H5
342	Etorixocib	H6
343	Etorixocib	H7
344	Etorixocib	H8
345	Etorixocib	H9
346	Etorixocib	H10
347	Etorixocib	H11
348	Etorixocib	H12
349	Etorixocib	H13
350	Etorixocib	H14
351	Etorixocib	H15
352	Etorixocib	H16
353	Etorixocib	H17
354	Etorixocib	H18

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
355	Etorixocib	H19
356	Etorixocib	H20
357	Etorixocib	H21
358	Etorixocib	H22
359	Etorixocib	H23
360	Etorixocib	H24
361	Etorixocib	H25
362	Etorixocib	H26
363	Etorixocib	H27
364	Etorixocib	H28
365	Etorixocib	H29
366	Etorixocib	H30
367	Etorixocib	H31
368	Etorixocib	H32
369	Etorixocib	H33
370	Etorixocib	H34
371	Etorixocib	H35
372	Etorixocib	H36
373	Etorixocib	H37
374	Etorixocib	H38
375	Etorixocib	H39
376	Etorixocib	H40
377	Etorixocib	H41
378	Etorixocib	H42
379	Etorixocib	H43
380	Etorixocib	H44
381	Etorixocib	H45
382	Etorixocib	H46
383	Etorixocib	H47
384	Etorixocib	H48
385	Etorixocib	H49
386	Etorixocib	H50
387	Etorixocib	H51

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
388	Etorixocib	H52
389	Etorixocib	H53
390	Etorixocib	H54
391	Etorixocib	H55
392	Etorixocib	H56
393	Etorixocib	H57
394	Etorixocib	H58
395	Etorixocib	H59
396	Etorixocib	H60
397	Etorixocib	H61
398	Etorixocib	H62
399	Etorixocib	H63
400	Etorixocib	H64
401	Etorixocib	H65
402	Etorixocib	H66
403	Etorixocib	H67
404	Etorixocib	H68
405	Etorixocib	H69
406	Etorixocib	H70
407	Etorixocib	H71
408	Etorixocib	H72
409	Etorixocib	H73
410	Etorixocib	H74
411	Etorixocib	H75
412	Etorixocib	H76
413	Etorixocib	H77
414	Etorixocib	H78
415	Etorixocib	H79
416	Etorixocib	H80
417	Etorixocib	H81
418	Etorixocib	H82
419	Etorixocib	H83
420	Etorixocib	H84

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
421	Lumiracoxib	H1
422	Lumiracoxib	H2
423	Lumiracoxib	H3
424	Lumiracoxib	H4
425	Lumiracoxib	H5
426	Lumiracoxib	H6
427	Lumiracoxib	H7
428	Lumiracoxib	H8
429	Lumiracoxib	H9
430	Lumiracoxib	H10
431	Lumiracoxib	H11
432	Lumiracoxib	H12
433	Lumiracoxib	H13
434	Lumiracoxib	H14
435	Lumiracoxib	H15
436	Lumiracoxib	H16
437	Lumiracoxib	H17
438	Lumiracoxib	H18
439	Lumiracoxib	H19
440	Lumiracoxib	H20
441	Lumiracoxib	H21
442	Lumiracoxib	H22
443	Lumiracoxib	H23
444	Lumiracoxib	H24
445	Lumiracoxib	H25
446	Lumiracoxib	H26
447	Lumiracoxib	H27
448	Lumiracoxib	H28
449	Lumiracoxib	H29
450	Lumiracoxib	H30
451	Lumiracoxib	H31
452	Lumiracoxib	H32
453	Lumiracoxib	H33

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
454	Lumiracoxib	H34
455	Lumiracoxib	H35
456	Lumiracoxib	H36
457	Lumiracoxib	H37
458	Lumiracoxib	H38
459	Lumiracoxib	H39
460	Lumiracoxib	H40
461	Lumiracoxib	H41
462	Lumiracoxib	H42
463	Lumiracoxib	H43
464	Lumiracoxib	H44
465	Lumiracoxib	H45
466	Lumiracoxib	H46
467	Lumiracoxib	H47
468	Lumiracoxib	H48
469	Lumiracoxib	H49
470	Lumiracoxib	H50
471	Lumiracoxib	H51
472	Lumiracoxib	H52
473	Lumiracoxib	H53
474	Lumiracoxib	H54
475	Lumiracoxib	H55
476	Lumiracoxib	H56
477	Lumiracoxib	H57
478	Lumiracoxib	H58
479	Lumiracoxib	H59
480	Lumiracoxib	H60
481	Lumiracoxib	H61
482	Lumiracoxib	H62
483	Lumiracoxib	H63
484	Lumiracoxib	H64
485	Lumiracoxib	H65
486	Lumiracoxib	H66

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
487	Lumiracoxib	H67
488	Lumiracoxib	H68
489	Lumiracoxib	H69
490	Lumiracoxib	H70
491	Lumiracoxib	H71
492	Lumiracoxib	H72
493	Lumiracoxib	H73
494	Lumiracoxib	H74
495	Lumiracoxib	H75
496	Lumiracoxib	H76
497	Lumiracoxib	H77
498	Lumiracoxib	H78
499	Lumiracoxib	H79
500	Lumiracoxib	H80
501	Lumiracoxib	H81
502	Lumiracoxib	H82
503	Lumiracoxib	H83
504	Lumiracoxib	H84
505	Deracoxib	H1
506	Deracoxib	H2
507	Deracoxib	H3
508	Deracoxib	H4
509	Deracoxib	H5
510	Deracoxib	H6
511	Deracoxib	H7
512	Deracoxib	H8
513	Deracoxib	H9
514	Deracoxib	H10
515	Deracoxib	H11
516	Deracoxib	H12
517	Deracoxib	H13
518	Deracoxib	H14
519	Deracoxib	H15

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
520	Deracoxib	H16
521	Deracoxib	H17
522	Deracoxib	H18
523	Deracoxib	H19
524	Deracoxib	H20
525	Deracoxib	H21
526	Deracoxib	H22
527	Deracoxib	H23
528	Deracoxib	H24
529	Deracoxib	H25
530	Deracoxib	H26
531	Deracoxib	H27
532	Deracoxib	H28
533	Deracoxib	H29
534	Deracoxib	H30
535	Deracoxib	H31
536	Deracoxib	H32
537	Deracoxib	H33
538	Deracoxib	H34
539	Deracoxib	H35
540	Deracoxib	H36
541	Deracoxib	H37
542	Deracoxib	H38
543	Deracoxib	H39
544	Deracoxib	H40
545	Deracoxib	H41
546	Deracoxib	H42
547	Deracoxib	H43
548	Deracoxib	H44
549	Deracoxib	H45
550	Deracoxib	H46
551	Deracoxib	H47
552	Deracoxib	H48

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
553	Deracoxib	H49
554	Deracoxib	H50
555	Deracoxib	H51
556	Deracoxib	H52
557	Deracoxib	H53
558	Deracoxib	H54
559	Deracoxib	H55
560	Deracoxib	H56
561	Deracoxib	H57
562	Deracoxib	H58
563	Deracoxib	H59
564	Deracoxib	H60
565	Deracoxib	H61
566	Deracoxib	H62
567	Deracoxib	H63
568	Deracoxib	H64
569	Deracoxib	H65
570	Deracoxib	H66
571	Deracoxib	H67
572	Deracoxib	H68
573	Deracoxib	H69
574	Deracoxib	H70
575	Deracoxib	H71
576	Deracoxib	H72
577	Deracoxib	H73
578	Deracoxib	H74
579	Deracoxib	H75
580	Deracoxib	H76
581	Deracoxib	H77
582	Deracoxib	H78
583	Deracoxib	H79
584	Deracoxib	H80
585	Deracoxib	H81

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
586	Deracoxib	H82
587	Deracoxib	H83
588	Deracoxib	H84
589	Rofecoxib	H1
590	Rofecoxib	H2
591	Rofecoxib	H3
592	Rofecoxib	H4
593	Rofecoxib	H5
594	Rofecoxib	H6
595	Rofecoxib	H7
596	Rofecoxib	H8
597	Rofecoxib	H9
598	Rofecoxib	H10
599	Rofecoxib	H11
600	Rofecoxib	H12
601	Rofecoxib	H13
602	Rofecoxib	H14
603	Rofecoxib	H15
604	Rofecoxib	H16
605	Rofecoxib	H17
606	Rofecoxib	H18
607	Rofecoxib	H19
608	Rofecoxib	H20
609	Rofecoxib	H21
610	Rofecoxib	H22
611	Rofecoxib	H23
612	Rofecoxib	H24
613	Rofecoxib	H25
614	Rofecoxib	H26
615	Rofecoxib	H27
616	Rofecoxib	H28
617	Rofecoxib	H29
618	Rofecoxib	H30

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
619	Rofecoxib	H31
620	Rofecoxib	H32
621	Rofecoxib	H33
622	Rofecoxib	H34
623	Rofecoxib	H35
624	Rofecoxib	H36
625	Rofecoxib	H37
626	Rofecoxib	H38
627	Rofecoxib	H39
628	Rofecoxib	H40
629	Rofecoxib	H41
630	Rofecoxib	H42
631	Rofecoxib	H43
632	Rofecoxib	H44
633	Rofecoxib	H45
634	Rofecoxib	H46
635	Rofecoxib	H47
636	Rofecoxib	H48
637	Rofecoxib	H49
638	Rofecoxib	H50
639	Rofecoxib	H51
640	Rofecoxib	H52
641	Rofecoxib	H53
642	Rofecoxib	H54
643	Rofecoxib	H55
644	Rofecoxib	H56
645	Rofecoxib	H57
646	Rofecoxib	H58
647	Rofecoxib	H59
648	Rofecoxib	H60
649	Rofecoxib	H61
650	Rofecoxib	H62
651	Rofecoxib	H63

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
652	Rofecoxib	H64
653	Rofecoxib	H65
654	Rofecoxib	H66
655	Rofecoxib	H67
656	Rofecoxib	H68
657	Rofecoxib	H69
658	Rofecoxib	H70
659	Rofecoxib	H71
660	Rofecoxib	H72
661	Rofecoxib	H73
662	Rofecoxib	H74
663	Rofecoxib	H75
664	Rofecoxib	H76
665	Rofecoxib	H77
666	Rofecoxib	H78
667	Rofecoxib	H79
668	Rofecoxib	H80
669	Rofecoxib	H81
670	Rofecoxib	H82
671	Rofecoxib	H83
672	Rofecoxib	H84
673	Meloxicam	H1
674	Meloxicam	H2
675	Meloxicam	H3
676	Meloxicam	H4
677	Meloxicam	H5
678	Meloxicam	H6
679	Meloxicam	H7
680	Meloxicam	H8
681	Meloxicam	H9
682	Meloxicam	H10
683	Meloxicam	H11
684	Meloxicam	H12

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
685	Meloxicam	H13
686	Meloxicam	H14
687	Meloxicam	H15
688	Meloxicam	H16
689	Meloxicam	H17
690	Meloxicam	H18
691	Meloxicam	H19
692	Meloxicam	H20
693	Meloxicam	H21
694	Meloxicam	H22
695	Meloxicam	H23
696	Meloxicam	H24
697	Meloxicam	H25
698	Meloxicam	H26
699	Meloxicam	H27
700	Meloxicam	H28
701	Meloxicam	H29
702	Meloxicam	H30
703	Meloxicam	H31
704	Meloxicam	H32
705	Meloxicam	H33
706	Meloxicam	H34
707	Meloxicam	H35
708	Meloxicam	H36
709	Meloxicam	H37
710	Meloxicam	H38
711	Meloxicam	H39
712	Meloxicam	H40
713	Meloxicam	H41
714	Meloxicam	H42
715	Meloxicam	H43
716	Meloxicam	H44
717	Meloxicam	H45

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
718	Meloxicam	H46
719	Meloxicam	H47
720	Meloxicam	H48
721	Meloxicam	H49
722	Meloxicam	H50
723	Meloxicam	H51
724	Meloxicam	H52
725	Meloxicam	H53
726	Meloxicam	H54
727	Meloxicam	H55
728	Meloxicam	H56
729	Meloxicam	H57
730	Meloxicam	H58
731	Meloxicam	H59
732	Meloxicam	H60
733	Meloxicam	H61
734	Meloxicam	H62
735	Meloxicam	H63
736	Meloxicam	H64
737	Meloxicam	H65
738	Meloxicam	H66
739	Meloxicam	H67
740	Meloxicam	H68
741	Meloxicam	H69
742	Meloxicam	H70
743	Meloxicam	H71
744	Meloxicam	H72
745	Meloxicam	H73
746	Meloxicam	H74
747	Meloxicam	H75
748	Meloxicam	H76
749	Meloxicam	H77
750	Meloxicam	H78

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
751	Meloxicam	H79
752	Meloxicam	H80
753	Meloxicam	H81
754	Meloxicam	H82
755	Meloxicam	H83
756	Meloxicam	H84
757	A chromene Cox-2 inhibitor	H1
758	A chromene Cox-2 inhibitor	H2
759	A chromene Cox-2 inhibitor	H3
760	A chromene Cox-2 inhibitor	H4
761	A chromene Cox-2 inhibitor	H5
762	A chromene Cox-2 inhibitor	H6
763	A chromene Cox-2 inhibitor	H7
764	A chromene Cox-2 inhibitor	H8
765	A chromene Cox-2 inhibitor	H9
766	A chromene Cox-2 inhibitor	H10
767	A chromene Cox-2 inhibitor	H11
768	A chromene Cox-2 inhibitor	H12
769	A chromene Cox-2 inhibitor	H13
770	A chromene Cox-2 inhibitor	H14
771	A chromene Cox-2 inhibitor	H15
772	A chromene Cox-2 inhibitor	H16
773	A chromene Cox-2 inhibitor	H17
774	A chromene Cox-2 inhibitor	H18

Example Number	Cox-2 Inhibitor	5-HT$_{1A}$ Receptor Modulator
775	A chromene Cox-2 inhibitor	H19
776	A chromene Cox-2 inhibitor	H20
777	A chromene Cox-2 inhibitor	H21
778	A chromene Cox-2 inhibitor	H22
779	A chromene Cox-2 inhibitor	H23
780	A chromene Cox-2 inhibitor	H24
781	A chromene Cox-2 inhibitor	H25
782	A chromene Cox-2 inhibitor	H26
783	A chromene Cox-2 inhibitor	H27
784	A chromene Cox-2 inhibitor	H28
785	A chromene Cox-2 inhibitor	H29
786	A chromene Cox-2 inhibitor	H30
787	A chromene Cox-2 inhibitor	H31
788	A chromene Cox-2 inhibitor	H32
789	A chromene Cox-2 inhibitor	H33
790	A chromene Cox-2 inhibitor	H34
791	A chromene Cox-2 inhibitor	H35
792	A chromene Cox-2 inhibitor	H36
793	A chromene Cox-2 inhibitor	H37
794	A chromene Cox-2 inhibitor	H38
795	A chromene Cox-2 inhibitor	H39
796	A chromene Cox-2 inhibitor	H40

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
797	A chromene Cox-2 inhibitor	H41
798	A chromene Cox-2 inhibitor	H42
799	A chromene Cox-2 inhibitor	H43
800	A chromene Cox-2 inhibitor	H44
801	A chromene Cox-2 inhibitor	H45
802	A chromene Cox-2 inhibitor	H46
803	A chromene Cox-2 inhibitor	H47
804	A chromene Cox-2 inhibitor	H48
805	A chromene Cox-2 inhibitor	H49
806	A chromene Cox-2 inhibitor	H50
807	A chromene Cox-2 inhibitor	H51
808	A chromene Cox-2 inhibitor	H52
809	A chromene Cox-2 inhibitor	H53
810	A chromene Cox-2 inhibitor	H54
811	A chromene Cox-2 inhibitor	H55
812	A chromene Cox-2 inhibitor	H56
813	A chromene Cox-2 inhibitor	H57
814	A chromene Cox-2 inhibitor	H58
815	A chromene Cox-2 inhibitor	H59
816	A chromene Cox-2 inhibitor	H60
817	A chromene Cox-2 inhibitor	H61
818	A chromene Cox-2 inhibitor	H62

Example Number	Cox-2 Inhibitor	5-HT_{1A} Receptor Modulator
819	A chromene Cox-2 inhibitor	H63
820	A chromene Cox-2 inhibitor	H64
821	A chromene Cox-2 inhibitor	H65
822	A chromene Cox-2 inhibitor	H66
823	A chromene Cox-2 inhibitor	H67
824	A chromene Cox-2 inhibitor	H68
825	A chromene Cox-2 inhibitor	H69
826	A chromene Cox-2 inhibitor	H70
827	A chromene Cox-2 inhibitor	H71
828	A chromene Cox-2 inhibitor	H72
829	A chromene Cox-2 inhibitor	H73
830	A chromene Cox-2 inhibitor	H74
831	A chromene Cox-2 inhibitor	H75
832	A chromene Cox-2 inhibitor	H76
833	A chromene Cox-2 inhibitor	H77
834	A chromene Cox-2 inhibitor	H78
835	A chromene Cox-2 inhibitor	H79
836	A chromene Cox-2 inhibitor	H80
837	A chromene Cox-2 inhibitor	H81
838	A chromene Cox-2 inhibitor	H82
839	A chromene Cox-2 inhibitor	H83
840	A chromene Cox-2 inhibitor	H84

Biological Assays

Evaluation of Cox-1 and Cox-2 activity *in vitro*:

[000246] The Cox-2 inhibiting agents of this invention exhibit Cox-2 inhibition *in vitro*. The Cox-2 inhibition activity of the compounds illustrated in the example above are determined by the following methods. The Cox-2 inhibition activity of the other Cox-2 inhibitors of the present invention may also be determined by the following methods.

Preparation of recombinant Cox baculoviruses:

[000247] Recombinant Cox-1 and Cox-2 are prepared as described by Gierse et al., [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine Cox-1 or human or murine Cox-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for Cox-1 and Cox-2 in a manner similar to the method of D.R. O'Reilly et al. (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2x108) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (107-108 pfu/mL) stocks of virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for Cox activity.

Assay for Cox-1 and Cox-2 activity:

[000248] Cox activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate Cox enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

Fast assay for Cox-1 and Cox-2 activity:

[000249] Cox activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate Cox enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 µM phenol, 1 µM heme, 300 µM epinephrine) with the addition of 20 µl of 100 µM arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C/room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

Evaluation of 5-HT_{1A} Activity *in vitro*

5-HT_{1A} Receptor Binding Profile:

[000250] Compounds are tested for binding to cloned human 5-HT_{1A} receptors stably transfected into CHO cells using [^{3}H]8-OH-DPAT as the

5-HT_{1A} radioligand (according to general procedure described in J. Dunlop *et al., J. Pharmacol. Tox. Methods, 40*:47-55 (1998)).

5-HT_{1A} Functional Activity Assay:

[000251] A clonal cell line stably transfected with the human 5-HT_{1A} receptor is utilized to determine the intrinsic activity of compounds (according to the general procedure described in J. Dunlop *et al., J. Pharmacol. Tox. Methods, 40*:47-55 (1998)). Compounds of the present invention are tested for their efficacy in antagonizing the ability of 10 nM 8-OH-DPAT to inhibit forskolin stimulated cAMP production in a concentration-related fashion.

Biological Evaluation:

[000252] A combination therapy of a Cox-2 inhibiting agent and a 5-HT_{1A} receptor modulator for the treatment or prevention of pain, inflammation, or an inflammation-related disorder in a mammal can be evaluated as described in the following tests.

Rat focal stroke model:

[000253] The efficacy of the compositions of the present invention for the prevention and treatment of focal stroke in rats can be determined according to the method described in Nogawa, S. *et al., J. of Neuroscience, 17(8)*:2748-2755 (1997).

Induction and Assessment of Collagen Induced Arthritis in Mice:

[000254] Arthritis is induced in 8-12 week old male DBA/1 mice by injection of 50 mg of chick type II collagen (CII) in complete Freunds adjuvant (Sigma) on day 0 at the base of the tail as previously described [J. Stuart, *Annual Rev. Immunol., 2*:199 (1984)]. Compounds are prepared as a suspension in 0.5% methylcellulose (Sigma, St. Louis, MO), 0.025% Tween 20 (Sigma). The Cox-2 inhibitors and the 5-HT_{1A} receptor modulator are administered alone or a Cox-2 inhibitor and 5-HT_{1A} receptor modulator in combination. The compounds are administered in non-

arthritic animals by gavage in a volume of 0.1 ml beginning on day 20 post collagen injection and continuing daily until final evaluation on day 55.

[000255] Animals are boosted on day 21 with 50 mg of collagen (CII) in incomplete Freunds adjuvant. The animals are subsequently evaluated several times each week for incidence and severity of arthritis until approximately day 56. Any animal with paw redness or swelling is counted as arthritic. Scoring of severity is carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as previously described [P. Wooley, *et al., Trans. Proc., 15*:180 (1983)]. The animals are measured for incidence of arthritis and severity in the animals where arthritis is observed. The incidence of arthritis is determined at a gross level by observing the swelling or redness in the paw or digits. Severity is measured with the following guidelines. Briefly, animals displaying four normal paws, *i.e.*, no redness or swelling are scored 0. Any redness or swelling of digits or the paw is scored as 1. Gross swelling of the whole paw or deformity is scored as 2. Ankylosis of joints is scored as 3.

Histological Examination of Paws:

[000256] In order to verify the gross determination of a non-arthritic animal, a histological examination is performed. Paws from animals sacrificed at the end of the experiment are removed, fixed and decalcified as previously described [R. Jonsson, *J. Immunol. Methods, 88*:109 (1986)]. Samples are paraffin embedded, sectioned, and stained with hematoxylin and eosin by standard methods. Stained sections are examined for cellular infiltrates, synovial hyperplasia, and bone and cartilage erosion.

[000257] All references cited in this specification, including without limitation all papers, publications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any

reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000258] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[000259] While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the methods, combinations and compositions of the present invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A composition comprising a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator.

2. The composition according to claim 1, wherein the amount of the Cox-2 inhibitor and the amount of the 5-HT_{1A} receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation or an inflammation-related disorder.

3. The composition according to claim 1, wherein the Cox-2 inhibitor comprises a non-steroidal anti-inflammatory drug.

4. The composition according to claim 3, wherein the Cox-2 inhibitor is selected from the group consisting of ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, prapoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenec, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acetyl salicylic acid, indometacin, piroxicam, tenoxicam, nabumetone, ketorolac, azapropazone, mefenamic acid, tolfenamic acid, diflunisal, podophyllotoxin derivatives, acemetacin, droxicam, floctafenine, oxyphenbutazone, phenylbutazone, proglumetacin, acemetacin, fentiazac, clidanac, oxipinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, flufenisal, sudoxicam, etodolac, piprofen, salicylic acid, choline magnesium trisalicylate, salicylate, benorylate, fentiazac, clopinac, feprazone, isoxicam, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

5. The composition according to claim 4, wherein the Cox-2 inhibitor comprises 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

6. The composition according to claim 1, wherein the Cox-2 inhibitor comprises a Cox-2 selective inhibitor.

7. The composition according to claim 6, wherein the Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, deracoxib, parecoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, and mixtures and prodrugs thereof.

8. The composition according to claim 7, wherein the Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, valdecoxib, rofecoxib, and mixtures thereof.

9. The composition according to claim 1, wherein the Cox-2 selective inhibitor comprises a chromene Cox-2 selective inhibitor.

10. The composition according to claim 1, wherein the 5-HT_{1A} receptor modulator comprises at least one compound selected from the group consisting of:
(R)-N-(1,3-benzodioxol-5-ylmethyl)-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine-3-carboxamide (AP-521), 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1H)-quinolinone (OPC-14523), 2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (DU-125530), 7-(4-methyl-1-piperazinyl)-2(3H)benzoxazolone, monohydrochloride (SLV-308), adatanserin, alnespirone, binospirone, buspirone, DU-127090, E-2101, eptapirone, flibanserin, gepirone, ipsapirone, lesopitron, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamidetrihydrochloride (WAY-100635), N-[3-(1,3-benzodioxol-5-yloxy)propyl]-2,3-dihydro-(2S)-1,4-benzodioxin-2-methanaminehydrochloride (MKC-242), repinotan, robalzotan, sarizotan, SLV-319, SUN-N4057, tandospirone, vilazodone, VML-670, xaliproden, ziprasidone, 6-hydroxy-buspirone, pyrazolidine derivative, heteroaryloxyethylamines, 5-hydoxytryptamine, 5-methoxytryptamine, buspirone, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), ipsaspirone, gepirone, SM23997, lysergic acid diethylamide, agonistic antibodies, piperazine derivatives, 8-(2-aminoalkoxy) fluorochroman

derivatives, abeo-ergoline derivatives, A-74283, AP-159, AZ 16596, 2- [[4-(2-methoxyphenyl)piperazin-1-yl] methyl] octahydroimidazo [1,5-a] pyridine-1,3-dione (B 20991), BMS 181100 (BMY 42569), BMS 181970, 1-methyl-4- [7-(4-chlorophenyl)methylaminocarbonyl] napththyl-piperazine (CP291952), (omega-piperazinylalkoxy) alkylenedioxybenzene (BP 554), E 5165, E 6265, ebalzotan, eltoprazine, F 11440, F 13714, flesinoxan, 2- [4-(3-phenylpyrrolidin-1-yl)butyl] -1,2-benzisothiazol-3(2H)-one 1,1-dioxide (LB 50016), LY 41, (+/-)-4-substituted-amino-6-substituted-1,3,4,5-tetrahydrobenz[c,d]inoles (LY 228729), LY 228730, LY 274600, LY 274601, LY 293284, 6-heterocyclyl-4-amino-1,3,4,5-tetrahydrobenz CD indoles (LY 297996), isoxazole derivatives (LY 315535), hetero-oxy alkanamines (LY 333068), LY 426965, LY 433221, MDL 72832, MDL 73975, NDL 249, nerisopam, Org 1301, 2-(2-oxo-hexahydropyrimidin-1-yl)propylaminomethyl- benzopyran (R 137696), RU 24969, 1-[[5-[[4-substituted-1-piperazinyl]methyl]-pyrrol-2-yl or furan-2-yl]methyl-2-piperidinones (RWJ 25730), S 14489, S 14506, S 14671, S 15535, S 15931, 8- [4- [N-(5-Acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)-Npropylamino] butyl] -8-azaspiro [4.5] decane-7,9-dione (S 23751), SDZ 216-525, SEP 109235, SR 59026, Sunepitron, UH 301, WAY 100135, WAY 100802, [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)amino]-methyl)piperidin-1-yl]-methadone] (F 13640), zalospirone, a pharmaceutically acceptable salt of any one of the compounds, and mixtures of two or more of the compounds.

11. The composition according to claim 1, wherein the 5-HT_{1A} receptor modulator comprises at least one compound that is selected from the group consisting of buspirone, gepirone, repinotan, tandospirone, xaliproden, ziprasidone, and mixtures thereof.

12. A method for the treatment or prevention of pain, inflammation, or inflammation-related disorder in a subject in need thereof,

comprising administering to the subject a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator.

13. The method according to claim 12, wherein the amount of the Cox-2 inhibitor and the amount of the 5-HT_{1A} receptor modulator together comprise a therapeutically effective amount for the treatment or prevention of pain, inflammation or an inflammation-related disorder in the subject.

14. The method according to claim 12, wherein the Cox-2 inhibitor comprises at least one non-steroidal anti-inflammatory drug that is selected from the group consisting of ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, prapoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenec, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acetyl salicylic acid, indometacin, piroxicam, tenoxicam, nabumetone, ketorolac, azapropazone, mefenamic acid, tolfenamic acid, diflunisal, podophyllotoxin derivatives, acemetacin, droxicam, floctafenine, oxyphenbutazone, phenylbutazone, proglumetacin, acemetacin, fentiazac, clidanac, oxipinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, flufenisal, sudoxicam, etodolac, piprofen, salicylic acid, choline magnesium trisalicylate, salicylate, benorylate, fentiazac, clopinac, feprazone, isoxicam, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

15. The method according to claim 12, wherein the Cox-2 inhibitor comprises a Cox-2 selective inhibitor.

16. The method according to claim 12, wherein the Cox-2 selective inhibitor comprises at least one compound that is selected from the group consisting of celecoxib, deracoxib, valdecoxib, parecoxib, lumiracoxib, rofecoxib, etoricoxib, meloxicam, and mixtures and prodrugs thereof.

17. The method according to claim 12, wherein the Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, parecoxib, rofecoxib, and mixtures thereof.

18. The method according to claim 12, wherein the 5-HT_{1A} receptor modulator comprises at least one compound selected from the group consisting of:
(R)-N-(1,3-benzodioxol-5-ylmethyl)-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine-3-carboxamide (AP-521), 1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-3,4-dihydro-5-methoxy-2(1H)-quinolinone (OPC-14523), 2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (DU-125530), 7-(4-methyl-1-piperazinyl)-2(3H)benzoxazolone, monohydrochloride (SLV-308), adatanserin, alnespirone, binospirone, buspirone, DU-127090, E-2101, eptapirone, flibanserin, gepirone, ipsapirone, lesopitron, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexanecarboxamidetrihydrochloride (WAY-100635), N-[3-(1,3-benzodioxol-5-yloxy)propyl]-2,3-dihydro-(2S)-1,4-benzodioxin-2-methanaminehydrochloride (MKC-242), repinotan, robalzotan, sarizotan, SLV-319, SUN-N4057, tandospirone, vilazodone, VML-670, xaliproden, ziprasidone, 6-hydroxy-buspirone, pyrazolidine derivative, heteroaryloxyethylamines, 5-hydoxytryptamine, 5-methoxytryptamine, buspirone, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), ipsaspirone, gepirone, SM23997, lysergic acid diethylamide, agonistic antibodies, piperazine derivatives, 8-(2-aminoalkoxy) fluorochroman derivatives, abeo-ergoline derivatives, A-74283, AP-159, AZ 16596, 2- [[4-(2-methoxyphenyl)piperazin-1-yl] methyl] octahydroimidazo [1,5-a] pyridine-1,3-dione (B 20991), BMS 181100 (BMY 42569), BMS 181970, 1-methyl-4- [7-(4-chlorophenyl)methylaminocarbonyl] napththyl-piperazine (CP291952), (omega-piperazinylalkoxy) alkylenedioxybenzene (BP 554), E 5165, E 6265, ebalzotan, eltoprazine, F 11440, F 13714, flesinoxan, 2- [4-(3-phenylpyrrolidin-1-yl)butyl]

-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (LB 50016), LY 41, (+/-)-4-Substituted-amino-6-substituted-1,3,4,5-tetrahydrobenz[c,d]inoles (LY 228729), LY 228730, LY 274600, LY 274601, LY 293284, 6-heterocyclyl-4-amino-1,3,4,5-tetrahydrobenz CD indoles (LY 297996), isoxazole derivatives (LY 315535), hetero-oxy alkanamines, (LY 333068), LY 426965, LY 433221, MDL 72832, MDL 73975, NDL 249, nerisopam, Org 1301, 2-(2-oxo-hexahydropyrimidin-1-yl)propylaminomethyl-benzopyran (R 137696), RU 24969, 1-[[5-[[4-substituted-1-piperazinyl]methyl]-pyrrol-2-yl or furan-2-yl]methyl-2-piperidinones (RWJ 25730), S 14489, S 14506, S 14671, S 15535, S 15931, 8- [4- [N-(5-Acetyl-3,4-dihydro-2H-1-benzopyran-3-yl)-Npropylamino] butyl] -8-azaspiro [4.5] decane-7,9-dione (S 23751), SDZ 216-525, SEP 109235, SR 59026, Sunepitron, UH 301, WAY 100135, WAY 100802, [(3-chloro-4-fluoro-phenyl)-[4-fluoro-4-{[(5-methyl-pyridin-2-ylmethyl)amino]-methyl)piperidin-1-yl]-methadone] (F 13640), zalospirone, and mixtures thereof.

or a pharmaceutically acceptable salt of the compound.

19. The method according to claim 12, wherein the 5-HT_{1A} receptor modulator comprises at least one compound that is selected from the group consisting of of buspirone, gepirone, repinotan, tandospirone, xaliproden, ziprasidone, and mixtures thereof.

20. The method according to claim 12, wherein the inflammation-related disorder is selected from the group consisting of central nervous system disorder, cognitive dysfunction, and glaucoma.

21. The method according to claim 20, wherein the central nervous system disorder is a disorder associated with stroke (ischemic or hemorrhagic) or ischemic brain injury.

22. The method according to claim 12, wherein the pain, inflammation or inflammation related disorder is selected from the group consisting of adjustment disorders, anxiety (mixed anxiety), mood (depressed), conduct disturbance, mixed anxiety and mood (conduct), addictive disorders, alcohol abuse, intoxication disorders, nicotine abuse,

psychoactive substances abuse, substance disorder, withdrawal syndromes, acute trauma, age associated mental disorders, learning disorders, Alzheimer's disease, agitation disorders, agitation in Alzheimer's disease, agitation in the elderly, aggressive behavior, aggressive behavior in Alzheimers disease, amyloidosis, aging / senile amyloidosis, hereditary amyloidosis, immunocyte derived amyloidosis, lichen amyloidosis, primary amyloidosis, reactive systemic amyloidosis, secondary amyloidosis, senile amyloidosis (Alzheimer's disease), amyotrophy & amyotripic lateral scherosis (ALS), ALS, anorexia nervosa, anxiety disorders, generalized anxiety disorder (GAD), social phobias, stress related diseases, apathy, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), autism, auto immune disorders, lupus erythematosis, multiple sclerosis, behavioral disturbances, agitation plus diminished cognition, bipolar I disorder, bipolar II disorder, bulimia nervosa, cardiovascular disorders, blood pressure modification, hypertension, hypotension, heart rate modification, chemotherapy-induced vomiting, chronic fatigue immune disorders (CFIDS), chronic fatigue syndrome (CFS), cognitive dysfunction, cortical dementias, mild cognitive impairment (MCI), Lewy Body dementia, vascular dementia, neurodegeneration, cognitive dysfunction resulting from stroke, ischemia, trauma, or surgical procedures, including coronary artery bypass surgery, cognition enhancement, conduct disorder, cyclothymia, delusional disorder, depression, adolescent depression, depression in Alzheimer's disease, general depression, minor depression, depression in Parkinson's disease, depression in diabetic neuropathy, dissociative disorders, developmental disorders, learning disabilities, language disorders, mental retardation, dementia, dementias associated with aging, illness, neurodegeneration and dyskensia, dysthymia, dystonia, eating disorders associated with anorexia nervosa, bulimia nervosa, obesity, epilepsy, or fibromyalgia syndrome (FMS), gastrointestinal disorders, irritable bowel syndrome, psychogenic effects and stress-related; growth retardation effects, endocrine, psychosocial and stress-related retardation, heart rate

modification, Huntington's chorea, hypertension, immune system disorders, immune system depression, impulse control disorders, incontinence, infectious neuropathy, AIDS, carpal tunnel syndrome, dementia, irritable bowel syndrome (IBS), constipative IBS, diarrhea-predominant IBS, inflammatory bowel disease (IBD), constipation-predominant IBD, diarrhea-predominant IBD, mixed states IBD, inhalation disorder, lactation inhibition, metabolic & chromosomal disorders, galactosemia phenylketonuria, fatty acid disorder, infantile nephropathic cystinosis, orthithrotranscarbamylase porphyria, migrane, mood disorders, atypical depression, bipolar disorder (including pychotic features), major depressive disorder, mania, seasonal affective disorder, movement disorders, athetosis, chorea, dyskinesia, dystonia, restless leg syndrome (RLS), tremor plus periodic limb movement (PLM), periodic limb movements of sleep (PLMS), Parkinson's disease, PLM, PLMS, progressive supranuclear palsy, stereotypy (various), torticollis, tic disorders, tremor; multisystemic atrophy (MSA), multiple sclerosis, neuroendocrine system disorders, neurodegenerative disorders, amyotrophy, amyotrophy diabetics, amyotrophic lateral sclerosis (ALS), Parkinson's disease, neurological disorders, neuropathy, diabetic neuropathy, peripheral neuropathy, neuroprotective effects for ischemic brain injury, neuroprotective effects for myocardial infarction, neuroprotective effects for spinal cord injury, neuroprotective effects for traumatic brain injury, neuroprotective effects for obesity, obsessive compulsive disorder (OCD), oncology related disorders, behavior abnormalities resulting from tumors or treatments, oppositional defiant disorder, pain disorders, acute pain, chronic pain, cluster headache, dysmenorrhea, labor pain, migraine pain, neuropathic pain, AIDs-related pain, AIDS-associated dementia, cancer-related pain, chemotherapeutic-induced pain, diabetic pain, post-herpetic neuralgia, radiation-induced pain, osteoarthritis flare, phantom limb pain, surgical pain, post-surgical pain, incisional pain, psychic pain, regional pain, abdominal pain, chronic back pain, complex-regional pain disorder, dental, face and mouth pain,

head pain, lower back and peripheral pain, rheumatoid arthritis pain, starting pain, systematic pain, connective tissue pain, musculoskeletal pain, nervous system pain, urogenital pain, uterine contraction pain, panic disorder, agoraphobia, peripheral neuropathy, personality disorders, phobias (simple), phobias of animals, phobias of closed spaces (claustrophobia), phobias of heights (acrophobia), phobias of public places (agoraphobia), social phobias, phobia of public eating, phobia of public embarrassment, phobia of public performance / speaking and using public lavatories, poop out syndrome, SSRI, post-traumatic stress disorder, progressive supranuclear palsy (PSP), prolactin plasma level disorders, psychotic disorders, brief psychosis, long duration psychosis, psychosis due to medical condition, restless leg syndrome (RLS), schizophrenias, delusional (paranoid) disorder, schizoaffective disorders, schizophreniform disorders, seasonal affective disorder, seizure disorders, epilepsy (partial), epilepsy (generalized), sexual dysfunction, sleep disorders, apnea, parasomnias, insomnia, narcolepsy, obstructive sleep disorder, disorders of circadian rhythm, enuresis, initiation, or maintenance, social phobias, social anxiety disorder, somatoform disorders, conversion, body, dysmorphic somatoform disorder, fibromyalgia syndrome (FMS), hypochondriasis, NOS, somatization, undifferentiated somatoform disorder, developmental disorders, stress disorders, acute stress disorder, chronic stress disorder, incontinence, spectrum disorders, stroke, suicidal behavior, thyroid stimulating hormone disorders (TSH), Tourette's syndrome, tooth-germ morphogenesis disorders, thermoregulation disorders, TSH modulating agent disorders, tic disorders, trauma, acute trauma, head trauma, vasospasms, vasoreactive headaches and violent behavior.

23. The method of claim 12, wherein the subject is a mammal.

24. A pharmaceutical composition for the treatment or prevention of pain, inflammation, or inflammation-related disorder, the

pharmaceutical composition comprising a Cox-2 inhibitor, a 5-HT_{1A} receptor modulator, and a pharmaceutically-acceptable excipient.

25. A kit that is suitable for use in the treatment or prevention of pain, inflammation, or inflammation-related disorder wherein the kit comprises a first dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a 5-HT_{1A} receptor modulator, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention or inhibition of pain, inflammation, or an inflammation-related disorder.

26. A method for the prevention or treatment of a neurologic disorder involving neurodegeneration in a subject that is in need of such prevention or treatment, the method comprising administering to the subject a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator.

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(57) Abstract: Compositions and methods to treat or prevent pain, inflammation, or inflammation-related disorder, as well as a neurologic disorder involving neurodegmeration in a subject that is in need of such prevention or treatment involve a combination of a Cox-2 inhibitor and a 5-HT_{1A} receptor modulator.

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,492,332 B1 (DEMOPULOS et al.) 10 December 2002(10.12.2002), column 2, lines 50-66 column 4, lines 41-63 and column 30, lines 30, lines 21-43.	1-26
X	US 5,840,746 A (DUCHARME et al.) 24 November 1998(24.11.1998), column 1, line 19 to column 13, line 25.	1-26

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